IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF TENNESSEE
NASHVILLE DIVISION

PLANNED PARENTHOOD OF TENNESSEE AND NORTH MISSISSIPPI; *et al.*, Plaintiffs, v. HERBERT H. SLATERY III, Attorney General of Tennessee, in his official capacity; *et al.*, Defendants.	Case No. 3:20-cv-00740 JUDGE CAMPBELL

DECLARATION OF COURTNEY A. SCHREIBER, M.D., M.P.H. IN SUPPORT OF PLAINTIFFS' MOTION FOR TEMPORARY RESTRAINING ORDER AND/OR PRELIMINARY INJUNCTION

Courtney A. Schreiber, M.D., M.P.H., declares and states as follows:

1. I am over 18 years of age and competent to make this declaration.

2. I submit this declaration in support of Plaintiffs' Motion for a Temporary Restraining Order and/or Preliminary Injunction preventing enforcement of Section 39-15-218 of H.B. 2263/S.B. 2196 (the "Act"), which would require physicians providing medication abortions to inform patients at least forty-eight hours prior to their having a medication abortion that "(1) [i]t may be possible to reverse the intended effects of a chemical abortion utilizing mifepristone if the woman changes her mind, but that time is of the essence; and

(2) [i]nformation on and assistance with reversing the effects of a chemical abortion utilizing mifepristone is available on the department of health website." Act § 39-15-218(e).[1]

3. I understand that a separate section of the Act requires that any private office, ambulatory surgical treatment center, other facility, or clinic that provided more than fifty "elective" abortions during the previous calendar year (other than abortions necessary to prevent the death of the patient) must "conspicuously post a sign" in numerous locations that states: "Recent developing research has indicated that mifepristone alone is not always effective in ending a pregnancy. It may be possible to avoid, cease, or even reverse the intended effects of a chemical abortion utilizing mifepristone if the second pill has not been taken. Please consult with a healthcare professional immediately." Act §§ 39-15-218(b),(d).

4. I understand that the sign must be "printed with lettering that is legible and at least three quarters of an inch (0.75") boldfaced type." Act § 39-15-218(c).

5. I understand that for private offices or ambulatory surgical treatment centers, this sign must be posted in each patient waiting room and patient consultation room used by patients on whom abortions are performed. Act § 39-15-218(d). For hospitals and other facilities, the sign must be posted in each patient admission area used by patients on whom abortions are performed. *Id.*

6. I understand that the Act requires that after the "first drug involved in the two-drug process is dispensed in a chemical abortion utilizing mifepristone, the physician or an agent

[1] The Act defines "chemical abortion" as "the use or prescription of an abortion-inducing drug dispensed with intent to cause the death of the unborn child." Act § 39-15-218(a)(2). I understand the use of the term "chemical abortion" in the Act to refer to medication abortion using mifepristone and misoprostol, as I describe in detail in this declaration. *See infra* at ¶¶ 18-24.

of the physician" must "provide written medical discharge instructions" to the patient which include the same statement reproduced in paragraph 3 of this Declaration. Act § 39-15-218(f).

7. I understand that within ninety days after the Act's effective date of October 1, 2020, the Tennessee Department of Health must publish and make available on its website materials "designed to inform the woman of the possibility of reversing the effects of a chemical abortion utilizing mifepristone if the woman changes her mind and information on and assistance with the resources that may be available to help reverse the effects of a chemical abortion." Act §§ 39-15-218(h),(i). I understand that these materials have not yet been published.

8. Finally, I understand that any physician who performs a medication abortion using mifepristone in violation of the Act would commit a felony criminal offense and be liable for damages in a civil lawsuit filed by the patient, the "father" of the fetus or embryo, or a minor or deceased patient's parents. Act §§ 39-15-218(j),(l). I also understand that medical facilities that violate the signage requirement may be fined $10,000 per day. Act § 39-15-218(k).

9. I am aware of a similar law that passed in Arizona several years ago but was later repealed, a similar law that recently passed in North Dakota and has been enjoined, and another similar law that recently passed in Oklahoma and has also been enjoined. Until the law in Arizona passed, I had never heard or read of "reversing" mifepristone or any other abortion-inducing drugs, and as an abortion provider and professor, I keep up to date with new research about medication abortion.

10. As I explain below, it is my opinion that the Act would force physicians to deviate from the best practice of medicine and the current medical evidence by providing information to patients that: (1) is medically unsupported, and is therefore false, misleading, and irrelevant to patients; (2) undermines the patient-provider relationship that is the cornerstone of the medical

profession in that it forces physicians to violate their ethical duty by providing false information to patients; and (3) poses real harm to both physicians and patients. I base these opinions on my expertise in the fields of obstetrics and gynecology; my experience in providing a broad range of reproductive health care to patients, including abortions; my expertise as a clinical researcher in the field of reproduction; and my familiarity with the body of scientific literature concerning medication abortion, including the few published papers regarding so-called "reversal."

My Expert Credentials

11. I am a board-certified obstetrician/gynecologist at the University of Pennsylvania Health System ("Penn Medicine") and a Professor of Obstetrics and Gynecology at the Perelman School of Medicine at the University of Pennsylvania. I am Chair of the Division of Complex Family Planning for the American Board of Obstetrics and Gynecology. I am also a Fellow of the American College of Obstetricians and Gynecologists ("ACOG").[2] At Penn Medicine and the Perelman School of Medicine, I serve as Chief of the Division of Family Planning, the Director of the Pregnancy Early Access Center, and Program Director of the Fellowship in Family Planning. I also serve as an attending physician at the Hospital of the University of Pennsylvania.

12. At Penn Medicine, I teach medical students as well as residents, including those training in obstetrics/gynecology and family medicine, among others, both didactically and clinically. Among the subjects I teach is abortion, including medication abortion and procedural abortion. In addition, I direct the Fellowship in Complex Family Planning at Penn, which involves teaching advanced family planning and abortion techniques to doctors who have completed their residencies and seek sub-specialization. I am an expert in the provision of abortion services, having provided this procedure to over 5,000 patients as an integral component

[2] ACOG is also known as the American Congress of Obstetricians and Gynecologists.

of my practice. In so doing, I use various approaches to abortion care, including medication abortion, vacuum aspiration, and dilation and evacuation. I provide general gynecology and expert contraceptive management as well as expert care in early pregnancy loss (or miscarriage), and I have been practicing in this way as an attending physician for fourteen years at the Perelman School of Medicine.

13. In addition to being an obstetrician/gynecologist, I hold a master's degree in public health with a concentration in epidemiology (the study of the incidence, distribution, and possible control of diseases and other factors relating to health). I also have expertise in the conduct of human-subjects research in reproduction.

14. A copy of my curriculum vitae ("CV") is annexed hereto as Exhibit A. As indicated on my CV, I have published over forty peer-reviewed research articles on a wide range of reproductive health issues. In addition, I have been the principal investigator or co-investigator on approximately fifty-five research studies relating to early pregnancy, sexually transmitted infections, abortion, and contraception.

15. I serve on the editorial board of the journal *Contraception*, and I am a reviewer for the *American Journal of Obstetrics and Gynecology*. I have also served as a reviewer for the journal *Pharmacoepidemiology*.

Abortion and the Science of Medication Abortion

16. Abortion is one of the safest and most common outpatient procedures performed in the United States. Approximately one in four women in the United States will have an abortion by age forty-five, and most who do so either already have children or are planning to

raise a family when they are older, financially stable, and/or in a supportive relationship with a partner.[3]

17. Carrying a pregnancy to term carries much higher risks of both morbidity and mortality than does abortion. The mortality rate associated with pregnancy in the United States is approximately fourteen times higher than the risks associated with abortion, and the complication rates for abortion are similar to, or lower than, complications associated with other outpatient procedures.[4]

18. As indicated above, there are both procedural and non-procedural (i.e., medication) abortion methods available. Medication abortion for early abortions (eleven weeks or fewer from the first day of the woman's last menstrual period (LMP)) is a safe method of ending a pregnancy by taking two medications, mifepristone (also known as RU-486 or by its trade name in the U.S., Mifeprex®) and misoprostol, that together cause the woman to undergo a pregnancy termination within a predictable period of time. In order to understand why the Act is grossly inconsistent with good medical practice and evidence-based care, it is important to understand the nature of medication abortion and how it is provided.

19. I understand that Plaintiffs provide medication abortion using an evidence-based regimen outlined in the 2016 Food and Drug Administration ("FDA") label for Mifeprex, which involves use of both mifepristone and misoprostol for patients with pregnancies at ten or fewer

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[3] *See Induced Abortion in the United States, Guttmacher Institute* (Sep. 2019), https://www.guttmacher.org/fact-sheet/induced-abortion-united-states; Jenna Jerman et al., *Characteristics of U.S. Abortion Patients in 2014 and Changes Since 2008* (May 2016), https://www.guttmacher.org/report/characteristics-us-abortion-patients-2014.

[4] Elizabeth G. Raymond & David A. Grimes, *The Comparative Safety of Legal Induced Abortion and Childbirth in the United States*, 119 Obstet. Gynecol. 215, 216-17 (2012).

weeks LMP. [5] The dosage, timing, and route of administration of this regimen has been endorsed by ACOG.[6] As set forth in the 2016 label, the protocol for administration of medication abortion is as follows: on day one, the patient takes 200 mg of mifepristone orally; twenty-four to forty-eight hours later, the patient takes 800 mcg of misoprostol buccally (in the cheek pouch) at a location of her choosing. The success rate for medication abortion in the United States under this protocol is 97.4%. As emphasized by the FDA in the updated 2016 label, this protocol has been demonstrated by clinical trials to be safe and extremely effective through seventy days or ten weeks LMP, and there is likewise evidence for the safe, effective use of a mifepristone-misoprostol regimen through seventy-seven days or eleven weeks LMP.[7] To date, more than four million women have used this method in the United States.[8]

20. This is the same combination of medications I use to provide medication abortion in my own practice and in my teaching.

21. When used in a medication abortion, mifepristone works by binding to receptors in the uterus and elsewhere, temporarily blocking the activity of the hormone progesterone and causing the pregnancy tissue and lining of the uterus to break down and separate from the uterine

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[5] I understand that Plaintiffs also provide medication abortion for patients with pregnancies up to eleven weeks LMP using mifepristone and misoprostol. This is also an evidence-based use. *See* American College of Obstetricians & Gynecologists and Society of Family Planning, *Practice Bulletin No. 225: Medication Abortion up to 70 Days of Gestation*, 136 Obstetrics & Gynecology 1, 4 (2020) (hereinafter "ACOG/SFP Guidelines").

[6] ACOG, *Practice Bulletin Number 143: Medical Management of First-Trimester Abortion,* 123 Obstet. Gynecol. 676 (Mar. 2014).

[7] *MIFEPRIX (Mifepristone) Tablets Label*, FDA https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf (2016) (detailing studies regarding the safe and effective use of Mifeprex through seventy days LMP); ACOG/SFP Guidelines, *supra* n.5.

[8] *Mifeprex Effectiveness & Advantages*, Danco Laboratories (last visited Sept. 11, 2019), https://www.earlyoptionpill.com/is-mifeprex-right-for-me/effectiveness-advantages/.

wall.[9] Mifepristone binds preferentially to progesterone receptors in the presence of progesterone because it has a higher affinity for the receptors, meaning that mifepristone binds more tightly to the receptors than progesterone does.[10] Mifepristone also triggers the release of endogenous prostaglandins (which can cause uterine contractions),[11] softens and opens the cervix,[12] and increases uterine contractility (capacity to contract).[13] Mifepristone is quickly absorbed, reaching peak concentrations in the blood about one to two hours after it is ingested.[14] Mifepristone is eliminated from the bloodstream slowly for the first seventy-two hours, then rapidly thereafter.[15]

22. In some percentage of pregnancies, particularly at the earliest stages, mifepristone alone will terminate the pregnancy. However, early research showed that mifepristone could not effectively be used alone as an abortion-inducing medication because it failed to work

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[9] Narendra N. Sarkar, *Mifepristone: Bioavailability, Pharmacokinetics, and Use-Effectiveness*, 101 Eur. J. of Obstetrics & Gynecology & Reprod. Biology 113, 115 (2002); Regine Sitruk-Ware & Irving Spitz, *Pharmacological Properties of Mifepristone: Toxicology and Safety in Animal and Human Studies*, 68 Contraception 409, 410-411 (2003); Beatrice Couzinet et al., *Termination of Early Pregnancy by the Progesterone Antagonist RU486 (Mifepristone)*, 315(25) N. Eng. J. Med. 1565, 1568 (1986).

[10] Sitruk-Ware & Spitz, *supra* n.9, at 410; Oskari Heikinheimo et al., *The Pharmacokinetics of Mifepristone in Humans Reveal Insights Into Differential Mechanisms of Antiprogestin Action*, 68 Contraception 421, 425 Table 1 (2003); Christian Fiala & Kristina Gemzell-Danielsson, *Review of Medical Abortion using Mifepristone in Combination with a Prostaglandin Analogue*, 74 Contraception 66, 68 (2006).

[11] Couzinet et al., *supra* n.9, at 1568; Remi Peyron et al., *Early Termination of Pregnancy with Mifepristone (RU 486) and the Orally Active Prostaglandin Misoprostol*, 328 N. Eng. J. Med. 1509, 1509 (1993).

[12] Couzinet et al., *supra* n.9, at 1568; Fiala & Gemzell-Danielsson, *supra* n.10, at 76.

[13] Couzinet et al., *supra* n.9, at 1568; Peyron et al., *supra* n.11, at 1509; Fiala & Gemzell-Danielsson, *supra* n.10, at 68; Sitruk-Ware & Spitz, *supra* n.9, at 411-12.

[14] Heikinheimo et al., *supra* n.10, at 422; Sarkar, *supra* n.9, at 114; Fiala & Gemzell-Danielsson, *supra* n.10, at 68.

[15] Sarkar, *supra* n.9, at 115.

sufficiently well on its own.[16] Subsequent research showed that the combination of mifepristone and a prostaglandin (misoprostol) work synergistically to terminate an early pregnancy with high efficacy.[17] Misoprostol taken buccally between twenty-four to forty-eight hours (or even up to seventy-two hours) after taking mifepristone induces uterine contractions. Mifepristone is also understood to increase the efficacy of misoprostol by weakening the endometrial lining and increasing the strength and efficacy of these contractions,[18] thereby increasing the likelihood that together they will result in pregnancy termination and expulsion.

23. Because taking these two drugs is part of a single regimen, "medication abortion" is commonly used to refer not to either mifepristone or misoprostol on their own but rather to the combination of the two drugs. Indeed, this is how the FDA approved the use of mifepristone for medication abortion.

24. As stated above, early research showed that when mifepristone was used alone to effect abortion, a significant number of pregnancies continued, making the drug inadequate for pregnancy termination on its own. It is difficult to estimate with accuracy the percentage of medication abortion patients who would have ongoing pregnancies after taking mifepristone alone. There are several reasons for this: (1) there are very few studies showing the proportion of pregnancies in which mifepristone alone caused embryonic or fetal demise; (2) almost all of those focused on pregnancies earlier than forty-nine days LMP;[19] (3) nearly all of those studies

[16] *See, e.g.*, *infra* n.21.

[17] Fiala & Gemzell-Danielsson, *supra* n.10, at 66-67.

[18] Fiala & Gemzell-Danielsson, *supra* n.10, at 66; Couzinet et al., *supra* n.9, at 1568.

[19] *See, e.g.*, Laszlo Kovacs et al., *Termination of Very Early Pregnancy by RU 486—An Antiprogestational Compound*, 29(5) Contraception 399 (1984) (including only women with pregnancies of forty-two days LMP or fewer).

involved higher doses of mifepristone than are currently used by most clinicians;[20] (4) more recent studies describe the efficacy of mifepristone only when combined with misoprostol, and most researchers do not study or compute success after mifepristone alone; and (5) large, population-based datasets are not available to analyze, since very few women elect to discontinue this medication abortion regimen after ingesting the mifepristone. But there is some evidence to suggest that up to 46% of women would have continuing pregnancies after taking mifepristone alone.[21] Additionally, data from trials looking at the efficacy of the mifepristone/misoprostol combination suggest that the rate of continued pregnancy increases as gestational age increases.[22]

The Lack of Credible Scientific Research to Support the Possibility of "Reversing" Medication Abortion

25. I am aware of a proposal by two physicians based in California, Dr. George Delgado and Dr. Mary Davenport, that physicians administer progesterone to "reverse" the effects of mifepristone in women who started the medication abortion regimen but did not take the misoprostol. Delgado and Davenport have published two papers that they claim support their proposal regarding the use of progesterone. These two papers are attached as Exhibits B and C.

26. In my medical and scientific opinion, the administration of progesterone to reverse the effects of mifepristone is experimental and unsupported by reliable scientific

[20] *See, e.g.*, Iain T. Cameron et al., *Therapeutic Abortion in Early Pregnancy with Antiprogestogen RU486 Alone or in Combination with Prostaglandin Analogue (Gemeprost)*, 34(5) Contraception 459 (1986) (studying total mifepristone dosage of 600mg, which is three times the current standard dosage).

[21] Zheng Shu-rang, *RU 486 (Mifepristone): Clinical Trials in China*, 149 Acta Obstericia Gynecologica Scand. Suppl. 19, 21 (1989).

[22] Beverly Winikoff et al., *Two Distinct Oral Routes of Misoprostol in Mifepristone Medical Abortion: A Randomized Control Trial*, 112(6) Obstetrics & Gynecology 1303, 1306 (2008).

evidence. ACOG and the Society of Family Planning ("SFP") recently issued a joint practice bulletin providing clinical management guidelines for obstetrician/gynecologists stating that "[t]here is no evidence that treatment with progesterone after taking mifepristone increases the likelihood of the pregnancy continuing."[23] The practice bulletin is attached as Exhibit D.

27. Thus, requiring physicians to tell patients that "it may be possible to reverse" the "intended effects" of a medication abortion utilizing mifepristone and refer them to the Department of Health website for "information on and assistance with reversing the effects of a chemical abortion utilizing mifepristone" could easily mislead patients into wrongly assuming that there are reliable data to support this practice. Doing so on the bases of the Delgado and Davenport papers, which provide no reliable scientific support for this practice, is unethical, and dangerous to the health and well-being of patients. ACOG previously published a statement on its website to this effect, explaining that "[c]laims regarding abortion 'reversal' treatment are not based in science and do not meet clinical standards," and that requiring physicians to inform patients about so-called "reversal" and to make referrals for such treatments "compromise[s] patient care and safety." That statement is attached here as Exhibit E. I agree with ACOG's determinations completely.

28. The two papers written by Dr. Delgado and his colleagues do not come close to providing scientifically valid support for the theory of medication abortion "reversal."

Delgado's 2012 paper fails to demonstrate that progesterone is effective to "reverse" mifepristone

29. The first paper, published in 2012 in the *Annals of Pharmacotherapy*, describes seven patients who took mifepristone and were then administered progesterone, using various routes of administration (oral, vaginal, and intramuscular). Of these patients, four carried their

[23] ACOG/SFP Guidelines, *supra* n.5, at 3.

pregnancies to term, two experienced abortions, and one was lost to follow-up.[24] At the end of the case series, Delgado and Davenport propose a protocol of regular intramuscular injections of doses of progesterone (200 mg) administered throughout the first trimester of pregnancy to reverse the effects of mifepristone.

30. As an initial matter, it is unclear why the authors chose to publish in the *Annals of Pharmacotherapy*, which is not known as being a journal that obstetrician/gynecologists or women's health clinicians regularly consult, and therefore the authors are unlikely to reach their target audience. By its title, *Annals of Pharmacotherapy* appears to be geared towards authors and readers who are pharmacologists and pharmaceutical scientists, rather than clinicians, and it is certainly not geared toward specialists in women's health or reproduction.

31. I was also surprised to see that the authors included clinical recommendations at the end of their paper, which the authors describe as containing "case reports."[25] Generally, case reports or series are used to identify new possible adverse effects of a drug or to identify a potential novel finding that the author is proposing for future study. Case reports or series are not considered sufficient evidence to support the safety, efficacy, or utility of a new treatment, nor are they considered the basis for providing or recommending a new course of treatment. Larger data sets with more rigorous study methodologies that include a sample size calculation and a control group are generally required in order to recommend practice change.

32. Control groups allow researchers to assess whether the change in a study participant's outcome was due to the treatment or some other factor. In a rigorous clinical trial with a control group, participants are randomly and blindly assigned to either a test group or a

[24] George Delgado & Mary L. Davenport, *Progesterone Use to Reverse the Effects of Mifepristone*, 46 Annals of Pharmacotherapy e36 (Dec. 2012).

[25] *Id.*

control group. The test group receives the treatment being tested, while the control group generally receives a placebo or another treatment known to be effective. Randomly assigning participants to the test or control group avoids other variables affecting the outcome, and blinding (meaning that both the participants and researchers do not know to which group the participant has been assigned) is intended to minimize potential biases that could otherwise be introduced. Because case reports or series lack these critical features, they generally are not considered to be of sufficient quality to support a change in treatment.

33. Not only do appropriately-sized data sets not exist on the topic of the 2012 paper, but the authors of this paper disclose that they based their proposed treatment protocol on a different protocol proposed in the separate context of miscarriage prevention, "the protocol of Hilgers," which itself does not appear to have been endorsed by any major medical organization or derived from any peer reviewed studies.[26] Furthermore, while the authors of the 2012 paper based their proposed protocol on the proposed use of progesterone in the context of miscarriage prevention, the effectiveness of using progesterone to prevent miscarriage has been significantly undermined: a recent randomized trial published in the *New England Journal of Medicine* demonstrated that progesterone does not prevent miscarriage among women who experience bleeding in early pregnancy.[27]

34. There are serious problems with attempting to draw any inferences from the Delgado paper. The number of patients reported—seven—is so small that no responsible researcher or physician would generalize from the outcomes reported. There is also a scarcity of relevant facts reported for each woman (such as exact gestational age of the pregnancy and the

[26] *Id.*

[27] Arri Coomarasamy et al., *A Randomized Trial of Progesterone in Women with Bleeding in Early Pregnancy*, 380 N. Eng. J. Med. 1815 (2019).

amount of mifepristone administered). The seventh patient was reported as lost to follow-up, and the outcome of her pregnancy is not included.

35. Moreover, as explained above, some women would be expected to have ongoing pregnancies after taking mifepristone alone, and this percentage would probably be higher the later in pregnancy a patient took the mifepristone. In the paper, the four patients who had a continued pregnancy took mifepristone later in gestation (between seven and ten or eleven weeks),[28] when mifepristone alone is known to be less effective at ending the pregnancy. Therefore, it is impossible to draw any conclusion about whether the progesterone injections had any effect at all on the patients' pregnancies.

36. In addition, it appears that all of the patients discussed in the paper as "successes" had confirmed embryonic or fetal cardiac activity before beginning progesterone treatment.[29] This fact—that all of these patients had pregnancies that had already withstood the initial effects of the mifepristone—itself indicates that these pregnancies were predisposed to continue and not demise. In other words, there is a selection bias in the study's small sample.

37. The paper also describes a variety of drug regimens provided to the patients, including different routes of administration (intramuscular and oral) of the progesterone, intervals between doses, and durations of treatment.[30] Some patients even continued taking progesterone into the seventh month of pregnancy. The reasons for these variations are not explained, nor is it explained why they used a variety of different formulations and doses, but

[28] Delgado & Davenport, *supra* n.24.

[29] The authors report that, in one case (of a patient who went on to miscarry), there was no documentation of cardiac activity before treatment, but do not explain why treatment was provided.

[30] Delgado & Davenport, *supra* n.24.

then recommend one particular regimen at the end of the paper. The "success" they report with a variety of regimens raises the likelihood that these women would have had ongoing pregnancies with placebo treatments, as well.

38. In short, no responsible physician would suggest, based on this paper, that "reversal" of mifepristone is possible. As ACOG has explained in the statement attached as Exhibit D, Dr. Delgado's claims of "reversing" mifepristone "are unproven and unethical," and his study does not amount to valid "scientific evidence that progesterone" can be used for these purposes.

Delgado's 2018 paper fails to demonstrate that progesterone is effective to "reverse" mifepristone

39. The second Delgado paper, published in 2018 in *Issues in Law and Medicine*, is, if anything, more problematic.[31] First, the journal in which the paper was published is once again noteworthy. *Issues in Law and Medicine* is known primarily as a legal policy journal, not as a publication for peer-reviewed scientific research. The journal's website states that it "is devoted to providing technical and informational assistance to attorneys, health care professionals, educators and administrators on legal, medical, and ethical issues arising from health care decisions."[32] This journal is not one that is utilized by clinicians or scientists for clinically relevant or actionable data. The journal's website further states that the journal "is co-sponsored by the National Legal Center for the Medically Dependent & Disabled, Inc. and the Watson Bowes Research Institute."[33] The Watson Bowes Research Institute, in turn, is affiliated with the

[31] George Delgado et al., *A Case Series Detailing the Successful Reversal of the Effects of Mifepristone Using Progesterone*, 33(1) Issues in L. & Med. 21 (2018).

[32] About, Issues in Law and Medicine (last visited Aug. 25, 2020), https://publons.com/journal/16314/issues-in-law-and-medicine/

[33] *Id*.

American Association of Pro-Life Obstetricians and Gynecologists (an anti-abortion advocacy organization), according to the latter's tax forms.[34] It is a journal with a political, not scientific, agenda.

40. The paper, entitled "A Case Series Detailing the Successful Reversal of the Effects of Mifepristone Using Progesterone," was published in 2018, but was subsequently withdrawn. Media reports indicate that the University of San Diego's Institutional Review Board ("IRB")[35] requested that the paper be withdrawn "because the wording regarding [Institutional Review Board] approval in the paper was ambiguous, leading many readers to incorrectly conclude that the University of San Diego's IRB had reviewed and approved the entire study," when it had in fact only approved a *retrospective* analysis (meaning, an analysis of data from past events) of pre-existing, patient de-identified data.[36]

41. When the paper was subsequently republished, the authors altered the description of their methods but not the results or discussion. Originally, the authors called the paper an

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[34] *See Form 990, Am. Ass'n of Pro-Life Obstetricians and Gynecologists* (2015), *available at* https://rewire.news/wp-content/uploads/2017/02/AAPLOG-990-2015.pdf.

[35] The professional norm and expectation is that research on human subjects should be approved by an IRB, which is a committee that performs an ethical review of proposed research. The purpose of IRBs is to protect human subjects of research. Some IRBs also review the design of a study to assess its potential to generate useful knowledge, and to ensure that the assessed potential benefits of the research outweigh the potential harms from a public health perspective. For these reasons, they are viewed as an important quality control mechanism; the government requires this step as a funding prerequisite, and reputable journals will not publish results obtained without IRB approval or exemption. I have conducted over 50 studies involving human subjects, and each one has been through the IRB-approval process. I can attest that this mechanism is not simply administrative but is vital to enabling the delicate balance between medical ethics and scientifically progressive research.

[36] *See*, *Study Claiming "Abortion Reversal" Is Safe and Effective Temporarily Withdrawn for Ethical Issues,* Retraction Watch (Jul. 17, 2018), https://retractionwatch.com/2018/07/17/study-claiming-abortion-reversal-is-safe-and-effective-temporarily-withdrawn-for-ethical-issues/ (alteration in original).

"observational case series," which is not actually an accepted or valid study design. The paper is also not a true "case series," because it was *prospective* in design—which is generally not the case with a case-series design. Similarly, the paper is not "observational" because instead of just observing the impact of a treatment on patients, the researchers actively enlisted participants to undergo an *experimental* intervention—here, the administration of progesterone after mifepristone. Worse still, the researchers administered the experimental intervention on patients without a control group—i.e., there was no group of similarly situated patients (meaning, patients who took mifepristone but not misoprostol or progesterone) to which the researchers could compare the patients who received progesterone to assess differences in birth outcomes. When the paper was republished, the authors described their methods differently, calling it a "retrospective analysis of clinical data," but did not alter their described results or discussion. It is unheard-of to withdraw a paper, rewrite its methods to describe an entirely different study design, and republish the remainder of the paper unchanged.[37]

42. No valid scientific conclusions can be drawn from the 2018 Delgado paper. It does not include a control group, and so no inference can be made about whether administration of progesterone has any effect (or the size of such effect, if any).[38] It would be inappropriate to draw any conclusions about causation from this paper.

43. Moreover, like the 2012 Delgado paper, the 2018 Delgado paper almost certainly overestimates the ongoing pregnancy rate among patients who received progesterone, making its

[37] Delgado et al., *supra* n.31.

[38] The best way to design a study in order to draw any inference about the impact of the exposure (here, progesterone), would be to take women receiving mifepristone, administer progesterone to those women who desire it, and then follow all women, regardless of exposure to progesterone, to their definitive pregnancy outcome. From such a study design, the authors would be able to compute the absolute risk and the relative risk or odds ratios of a continuing pregnancy with and without exposure to progesterone. Dr. Delgado's papers do none of this.

results unreliable. Specifically, women in the paper were administered progesterone only *after* ultrasound was used to confirm ongoing fetal cardiac activity after taking mifepristone (except in an unknown number of instances in which pre-administration ultrasound was not readily available). The fact that the data consisted primarily of women whose pregnancies had already withstood the effects of mifepristone means that the authors were reporting on pregnancies that were already predisposed to continue. The authors generously describe this as a "confounding variable," but the paper does not adequately account for its significance or attempt to statistically control for this as a confounding variable, as any valid scientific research study would do.[39]

44. Additionally, as with Dr. Delgado's 2012 paper, the heterogeneity of the delivery systems described in the 2018 paper further limits any interpretation of the results. The paper lists ten different progesterone regimens, which were not administered by study investigators following a research protocol, but by a dispersed group of clinicians.

45. The paper's ethics are likewise troubling. Because there is no specified regimen being assessed here, women were subjected to doses and routes of progesterone without any clinically actionable outcome gained. There is no sample size calculation provided, so it is entirely possible that more women were exposed than necessary to provide a statistically significant difference from the expected number of live births after mifepristone alone. Were women reimbursed for their time and trouble? Were these women coerced? As a clinician and as an investigator, this paper is deeply troubling on many levels.

46. As stated above, the 2018 Delgado paper does not use a control group; participants were not randomly and blindly assigned to either a control group or a treatment

[39] Delgado et al., *supra* n.31.

group. This makes it virtually impossible to infer from the paper whether treatment with progesterone played any role in participants' continued pregnancies.

47. The paper also lacks a scientifically valid use of what is known as a "historical control group." A study using a historical control is one in which there is no concurrent control group—meaning there is no group of participants who receive a placebo, no treatment, or a standard treatment concurrently while the experimental group receives the treatment being studied. Instead, the researchers select a population of patients who were studied previously, and the data from those previously studied patients make up the data for the historical control group. The outcomes from the treatment group are compared against the data for the patients whom the researchers chose as the historical control group. Because the researchers select which patients are included in the historical control group, these studies, by definition, do not have randomization and blinding. They are therefore much more susceptible to the introduction of bias. Such studies can be useful to prompt further study, but they are generally not sufficient by themselves to support a change in practice.

48. Moreover, if a historical control is to be used in a study, it is important that details about the population that is included in the historical control group be well documented and understood so that researchers can ensure that the control patients are as similar as possible to the patients who receive the treatment. The researchers should ensure that whether the participant received the treatment is the only variance between the participants selected for the historical control group and those selected for the treatment group. However, the 2018 Delgado paper did not follow this approach. Instead, the paper simply "selected a 25% embryo or fetus survival rate, if mifepristone alone is administered, as a control. . . ."[40] That is not a proper historical

[40]Delgado et al., *supra* n.31., at 6.

control. Additionally, as discussed below, the 25% number likely underestimates the true rate of continuing pregnancy in the historical population of patients who received mifepristone alone.

49. Finally, as discussed, a study using a historical control group is generally not sufficient to support a change in practice. To the extent any potential conclusions about the efficacy of the proposed treatment might be inferred from a study using a historical control group, it would only be where the researchers find a vastly larger difference in outcome between the historical control group and the treatment group than they would look for in a study using a concurrent control group. The 2018 Delgado paper does not consider this factor at all. In my opinion, even if the 2018 Delgado paper were a proper use of a historical control group (and as explained, it is not), any difference in outcome is not sufficiently significant to draw any conclusions from the paper.

Systematic review of research on mifepristone "reversal" establishes that there is insufficient evidence to support its effectiveness

50. Research and analyses published over the last few years confirm that both Delgado publications are inherently flawed and unsupported by the full body of scientific research on mifepristone and progesterone. A systematic review of the research on mifepristone "reversal," published in 2015 in the highly respected journal *Contraception*, demonstrated that evidence is insufficient to determine whether treatment with progesterone after mifepristone results in a higher proportion of continuing pregnancies compared to expectant management.[41] This article is attached as Exhibit F. Similarly, an article published in 2018 in the *New England Journal of Medicine*, the most widely read, cited, and influential medical journal in the world, compared the data from the 2018 Delgado and Davenport paper to the only study of the rate of

[41] Daniel Grossman et al., *Continuing Pregnancy After Mifepristone and "Reversal" of First-Trimester Medical Abortion: A Systematic Review*, 92(3) Contraception 206 (2015).

continuing pregnancy after the relevant dose of mifepristone (200 mg), and found that the confidence intervals around the point estimates overlap for women who do and do not use progesterone supplementation after using mifepristone. In essence, there is no evidence at all that progesterone administration after mifepristone use is effective at reversing, avoiding, or ceasing mifepristone's effects.[42] This article is attached as Exhibit G.

51. Delgado and Davenport published their own purported "systematic review" of the literature on mifepristone "reversal" in *Issues in Law & Medicine* in 2017, but like their other papers, it too is flawed.[43] Delgado and Davenport's review criticizes the review by Grossman et al. published in *Contraception* for including several studies "that did not assess abortion failures with ultrasound to verify if living embryos were present, or had other faulty criteria" despite the fact that Grossman et al. were in fact able to assess the number of continuing pregnancies in these studies. Meanwhile, Delgado and Davenport provide no rationale for excluding these studies from their review. Delgado and Davenport's review ultimately falls victim to several well-known errors in poorly conducted systematic reviews and meta analyses, including selective reporting, which occurs when the reporting of a subset of outcomes and analyses in the systematic review is based only on the results of the studies and does not take into account differences in the methods or populations included.[44] Finally, it appears that the purpose of this review was to compute the baseline rate of continuing pregnancy without progesterone

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[42] Daniel Grossman & Kari White, *Abortion "Reversal"—Legislating without Evidence*, 379(16) N. Eng. J. Med. 1401 (2018).

[43] Mary L. Davenport et al., *Embryo Survival after Mifepristone: A Systematic Review of the Literature*, 32(1) Issues in L. & Med. 3 (2017).

[44] Matthew J. Page et al., *Bias Due to Selective Inclusion and Reporting of Outcomes and Analyses in Systematic Reviews of Randomised Trials of Healthcare Interventions*, 1(10) Cochrane Database Syst. Rev. (Oct. 2014).

intervention in the population to inform Delgado's then-upcoming 2018 paper. But their statistical analysis of the papers they reviewed is flawed because the 25% number they cite in the paper as a "control" likely *underestimates* the true rate of continuing pregnancy in the population, with the effect that they *overestimated* the effectiveness of progesterone treatment to "reverse" abortion in their 2018 paper.[45]

Delgado's papers do not provide evidence upon which to base a treatment regimen

52. For all these reasons, the two flawed Delgado papers do not provide evidence upon which to base a treatment regimen. At a very practical level, progesterone injections are painful and expensive, and as explained below, they carry safety risks. It is unethical to recommend a treatment that causes pain, potential economic hardship, and safety risks when there is insufficient evidence of benefit to patients.

53. Indeed, even Delgado and Davenport in their 2012 paper conclude that "*if* further [clinical] trials confirm the success without complications of this or similar protocols, it should become the standard of care" and that currently physicians "may not want" to provide this treatment and only some physicians may be "comfortable" doing so.[46] These statements appear to be an acknowledgement (although insufficient) by the authors that their proposal requires an actual scientific investigation to determine safety and efficacy before it could be considered as a treatment. The 2018 paper similarly acknowledges that only "randomized controlled trials" can "confirm which mode of delivery, dose and duration of progesterone therapy is most efficacious

[45] *See* Delgado et al., *supra* n.31, at 24. To be appropriately conservative in preparation for the planned 2018 paper, the authors instead should have focused on the upper-bound 95% confidence interval around each study's point estimate of the rate of continuing pregnancy. *See* T.V. Sakpal, *Sample Size Estimation in Clinical Trial*, 1(2) Perspectives in Clinical Research 67 (Apr. 2010).

[46] Delgado & Davenport, *supra* n.24 (emphasis added).

and carries the least burden for the patient."[47] As described in the *New England Journal of Medicine* editorial regarding the now disproven use of progesterone to help reduce the risk of miscarriage, changes in clinical practice based upon observational studies alone (of which a case series is the least rigorous) have repeatedly been later proven to be misguided, and these findings need to be confirmed (or disproven) with more rigorous study designs.[48]

54. Further investigation would be especially necessary here because of the pharmacodynamics and pharmacokinetics of the competing medications. Given how high natural progesterone levels are in pregnancy already, it is unlikely that high doses of exogenous progesterone, sometimes beginning several days after the patient ingested the mifepristone and continuing throughout the first trimester of her pregnancy (or beyond), could reverse the effects of mifepristone. As explained above, mifepristone already outcompetes the body's natural progesterone (which is at very high levels in pregnancy, naturally), binds tightly to progesterone receptors within hours of being ingested, and acts quickly and most potently over a time-limited period of about seventy-two hours. For this reason, I would not expect that exogenous progesterone could have any effect once the mifepristone has started acting or that there would be any reason to further elevate a patient's (already high in pregnancy) progesterone levels long after the mifepristone has ceased blocking progesterone receptors, and one would need empiric evidence showing otherwise to credit an implausible theory. Further study would be required since, to date, sufficient data do not exist to make conclusive statements.

55. Further, as mentioned above in paragraph 33, recent research on the use of progesterone supplementation during pregnancy by Coomarasamy et al. calls into question its

[47] Delgado et al., *supra* n.31, at 29.

[48] *See* Green, *infra* n.50.

effectiveness in increasing the likelihood that a woman will carry a fetus to term. Specifically, a large, randomized, double-blind, placebo-controlled trial of progesterone use in over four thousand women with threatened miscarriages before twelve weeks of gestation found that the incidence of live births was the same in the group of women who received progesterone and the group that did not.[49] In addition, in an accompanying editorial in the *New England Journal of Medicine,* the following statement is made: "In retrospect, it is likely that the initial rationale for hormonal therapy—that is, the observed fall in pregnancy hormone levels before pregnancy loss—was, in fact, a consequence rather than a cause of pregnancy failure. The subsequent enthusiasm for hormonal therapy was driven by overestimation of the incidence of pregnancy loss in the absence of therapy and by reports of seeming success in uncontrolled case series."[50] This statement not only underscores the flaws with the concept of progesterone "rescue therapy" but also highlights the dangers of over-interpretation of data derived from case series, the methodology Delgado and associates claim to have used.[51] Clearly, if medical experts cannot draw strong scientific conclusions from a case series, Tennessee should not be legislating the practice of medicine based on the data they produce.[52]

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[49] Coomarasamy et al., *supra* n.27.

[50] Michael F. Green, Editorial, *Progesterone for Threatened Abortion*, 380(19) N. Eng. J. Med. 1867 (2019).

[51] While the Coomarasamy et al. study suggested some clinically significant benefit for the small group of patients in the sample that had three or more previous miscarriages (i.e. recurrent miscarriages), the study did not draw any conclusions about the potential benefit to these patients. Patients with recurrent miscarriages are commonly understood to have distinct and even unique medical etiology, as compared to other patients. *See, e.g.*, Mercy Y. Laurino, et al. *Genetic Evaluation and Counseling of Couples with Recurrent Miscarriage: Recommendations of the National Society of Genetic Counselors*, 14(3) J. of Genetic Counseling (Jun. 2005).

[52] Even if the hypothesis that sufficient quantities of exogenous progesterone can outcompete mifepristone was established, the message that it "may be possible to reverse" the intended effect of mifepristone is inaccurate and misleading. Mifepristone binds tightly to progesterone receptors. If it were shown that exogenous progesterone could outcompete mifepristone and bind

There are no reliable resources for medication abortion "reversal"

56. The Act requires the Tennessee Department of Health website to post information on resources that may be available to assist with medication abortion "reversal." Other than the two published Delgado papers, the only other source for information supporting medication abortion "reversal" about which I am aware is the Abortion Pill Reversal website and hotline that Drs. Delgado and Davenport founded, called abortionpillreversal.com.

57. The website states that "Abortion Pill Rescue" is a program of Heartbeat International,[53] a "network of pro-life pregnancy resource centers"[54] whose mission "is to make abortion unwanted today and unthinkable for future generations."[55] It appears that Delgado and Davenport are Medical and/or Research Advisors to Abortion Pill Rescue and there is a "network" of "professional healthcare providers" available to assist women who call their hotline.[56]

58. The website represents that there is a treatment that is "effective" in reversing abortion, which is a completely unproven claim. It states, "CAN THE ABORTION PILL BE REVERSED? The simple answer is yes! If done in time. There is an effective process called

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to the receptors, this would not be "reversing," "ceasing," or "avoiding" mifepristone or its effects. Rather, it would be overcoming the action of mifepristone. The term "reversal" in this context is thus a complete misnomer and is misleading and confusing to patients.

[53] *About Us*, Abortion Pill Reversal / Abortion Pill Rescue (2020), https://www.abortionpillreversal.com/about/our-team.

[54] *Frequently Asked Questions about Heartbeat International*, Heartbeat International (2020), https://www.heartbeatinternational.org/about-us/faqs#:~:text=is%20Heartbeat%20International%3F-,A.,to%20provide%20alternatives%20to%20abortion.

[55] *Our Passion*, Heartbeat International (2020), https://www.heartbeatinternational.org/about/our-passion.

[56] Abortion Pill Reversal, *supra* n.53.

abortion pill reversal that can reverse the effects of the abortion pill and allow you to continue your pregnancy, but time is of the essence."[57] This statement is false. It also states: "By giving extra progesterone, we hope to outnumber and outcompete the mifepristone in order to reverse the effects of mifepristone."[58] This conjecture has not been established and, based on the relative binding affinities and the other information described above, is unlikely to be true. The website lists the side-effects of mifepristone as a major section, which is not only irrelevant to their mission, but the side effects listed include additional false claims.[59] Finally, the website claims that "there have been many successful reversals," and that it "may not be too late" to reverse an abortion even after seventy-two hours,[60] which is highly misleading. It also goes against ACOG's recommendations. All told, this website conveys Abortion Pill Reversal's ideologically based agenda and is dangerous. It is replete with misinformation about mifepristone, and indicates the organization's intention to sow doubt in the patient's mind about the treatment protocol she and her physician have chosen. No physician practicing evidence-based medicine would refer a patient to this website.

Potential Safety Risks of Medication Abortion "Reversal"

Concerns about progesterone

59. Although progesterone is considered a low-risk medication, it does carry risks. Progesterone has been associated with maternal complications such as depression, cholestatic

[57] *Can the Abortion Pill be Reversed?* Abortion Pill Reversal / Abortion Pill Rescue (2020), https://www.abortionpillreversal.com/abortion-pill-reversal.

[58] *Reversal FAQ,* Abortion Pill Reversal / Abortion Pill Rescue (2020), https://www.abortionpillreversal.com/abortion-pill-reversal/faq.

[59] *How it Works*, Abortion Pill Reversal / Abortion Pill Rescue (2020), https://www.abortionpillreversal.com/how-it-works

[60] *Abortion Pill Reversal*, *supra* n.58.

jaundice, and hypertension. And while some data support the general safety of progesterone in pregnancy, there are also some studies that have raised concerns about a possible association with second-trimester miscarriage and stillbirth in pregnancies exposed to certain exogenous progesterone preparations.[61] Investigators also have reported associations with hypospadias, a defect in the male infant's genitalia, occurring in the male infants born to women who used progestins (synthetic or pharmacologic progesterones) during pregnancy.[62] While none of these data are conclusive, they are enough to raise concern in the absence of proven benefit. At a minimum, the safety of administering high-dose progesterone has not been adequately studied in this population or for this indication.

60. Even absent concerns about high-dose progesterone, I am also concerned about possible future complications to the pregnancy caused by the mifepristone alone, as well as a combination of mifepristone and progesterone. While mifepristone is not established to be teratogenic (meaning disruptive of embryonic/fetal development), neither mifepristone nor high doses of progesterone has been conclusively shown to be safe for fetal development, and the combined effect of the two has not been studied or even considered at all. It is entirely possible this regimen could cause harm to the fetus, including birth defects, and almost impossible that it would be acceptable per current federal standards—outlined in the Code of Federal Regulations Part 46, Protection of Human Subjects, Research Involving Pregnant Women or Fetuses[63]—

[61] Paul J. Meiss et al., *Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate*, 348 N. Eng. J. Med. 2379, 2382 (2003).

[62] Suzan L. Carmichael et al., *Maternal Progestin Intake and Risk of Hypospadias*, 159(10) Archives of Pediatric & Adolescent Med. 957 (2005).

[63] 45 C.F.R. § 46.204.

without intensive data safety and monitoring board oversight. There is no mention of such oversight in the Delgado publications.

Potential safety risks of discontinuing the mifepristone-misoprostol combined regimen

61. As explained above, medication abortion is a regimen of two medications: mifepristone and misoprostol. Indeed, the FDA has approved the use of mifepristone for medication abortion in combination with misoprostol.

62. This two-drug regimen is both extremely effective and extremely safe. Studies have shown that major complications—e.g., heavy bleeding or serious infection—occur in approximately 0.3% of medication abortion patients.[64] Medication abortion is safer than Tylenol.

63. Recent research, however, shows that there are serious safety concerns for patients who begin the medication abortion regimen by taking mifepristone but do not complete the regimen by taking misoprostol. Researchers at the University of California, Davis Medical Center, led by Dr. Mitchell Creinin, conducted a study to test the "reversal" hypothesis in the Delgado papers. The purpose of the study was to evaluate continuing pregnancy rates, safety, and side effects of high-dose oral progesterone in patients who used mifepristone alone without misoprostol. Unlike the Delgado papers, the Creinin study was a randomized, double-blind, placebo-controlled trial; it had IRB approval; and it was published in a prestigious, peer-reviewed journal, *Obstetrics & Gynecology*.[65]

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[64] Ushma D. Upadhyay et al., *Incidence of Emergency Department Visits and Complications After Abortion*, 125(1) Obstetrics & Gynecology 175 (Jan. 2015); Daniel Grossman and Kate Grindlay, *Safety of Medical Abortion Provided Through Telemedicine Compared With In Person*, 130(4) Obstetrics & Gynecology 778 (Oct. 2017).

[65] Mitchell D. Creinin et al., *Mifepristone Antagonization With Progesterone to Prevent Medical Abortion: A Randomized Controlled Trial*, 135(1) Obstetrics & Gynecology 158 (Jan. 2020).

64. The researchers enrolled participants who were pregnant, wanted abortions, were eligible for medication abortion, and were willing to delay their abortion by approximately two weeks. Participants took 200 mg of mifepristone and were then randomly allocated into a progesterone group and a placebo group. Participants in the progesterone group were instructed to take 800 mg of progesterone daily for three days beginning twenty-four hours after mifepristone, then 400 mg of progesterone daily for the remainder of the time they were in the study. Participants in the placebo group received placebos. Participants who had ongoing pregnancy after approximately two weeks received procedural abortions.[66]

65. The researchers halted the study after enrolling only twelve participants, due to serious safety concerns with continuing the study. Three of the twelve participants had severe, brisk hemorrhaging and had to be taken by ambulance to an emergency room. Of those three patients, one had such severe bleeding that she had to receive a blood transfusion. These three patients came from both the progesterone population and the placebo population. This suggests that the patients' hemorrhaging resulted from not following the medication abortion two-drug regimen, i.e., from using mifepristone alone and not in combination with misoprostol.[67]

66. The study raises serious safety concerns about not completing the medication abortion two-drug combination regimen. ACOG and SFP have issued a practice bulletin cautioning that the "limited available evidence suggests that use of mifepristone alone without subsequent administration of misoprostol may be associated with an increased risk of hemorrhage."[68] Yet this is exactly what Delgado's "reversal" treatment calls for. And Delgado's "reversal" hypothesis is based on his two flawed papers, neither of which reports any outcome

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[66] *Id.*

[67] *Id.*

[68] ACOG/SFP Guidelines, *supra* n.6, at 3.

for those patients who did not have continuing pregnancies after taking mifepristone but not misoprostol.

67. This study also confirms the dangers of performing unmonitored experiments such as following Delgado's "reversal" treatment. When a study is properly monitored, as the Creinin study was, the researchers can halt the study if safety concerns arise. It is especially inappropriate for Tennessee to enact the Act to encourage patients to participate in an experiment lacking the appropriate rigorous safety-monitoring protocols.

Delgado's Research is Unethical and Unprofessional

68. I also have serious concerns about what Dr. Delgado and his colleagues are doing from the perspective of scientific investigation. In my opinion, their activities amount to research on human subjects as it is commonly understood and as it is defined by the United States Department of Health and Human Services: "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."[69] I base this assessment on their own claims in their two published papers, as well as on media reports and statements, which indicate that these physicians are providing various experimental progesterone protocols to hundreds of women (with no indication of proper informed consent, ethical review, or data collection/publication), analyzing the results, and discussing these results publicly (and misleadingly) as supporting the efficacy and safety of their proposed experimental progesterone protocols.[70]

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[69] 28 C.F.R. § 46.102(d).

[70] Shannon Firth, *Reversing Abortion Pill: Can It Be Done?*, MedPage Today (Feb. 24, 2015), http://www.medpagetoday.com/OBGYN/GeneralOBGYN/50164 ("Of the 223 women who have received progesterone, 127 cases succeeded, according to a fact sheet Delgado shared."); Colette Wilson, *Interview: Reversing the Effects of RU-486*, Lifeline Newsletter (Life Legal Defense Foundation, Napa, CA) Vol. XXIV, No. 1 (Winter 2014), *available at*: http://lldf.org/interview-reversing-effects-ru486/ ("Dr. Delgado: We have established an exciting program called APR

69. Dr. Delgado's and his colleagues' approach also is contrary to ACOG Guidelines on Innovative Practice, which strongly warn against generalizing treatment practices before they have been subjected to rigorous study.[71] As these guidelines explain, there is a risk that, without this control, practices may become widely accepted even though they are ineffective. This proved to be the case, for example, with "[b]ed rest or home uterine activity monitoring for the prevention of prematurity," "[b]one marrow transplant for breast cancer," and "[d]iethylstilbestrol or paternal antigen sensitization for the prevention of recurrent miscarriage."[72] There is also a risk that unstudied treatments may carry "small but potentially important risks" that are not immediately apparent from an initial small sampling of experimental patients; past examples of such treatments include "[l]imb reductions associated with early chorionic villus sampling" and "[s]ex chromosome abnormalities associated with intracytoplasmic sperm injection used in assisted reproductive technology."[73]

70. For all the reasons above, in my opinion, the research that Dr. Delgado and his colleagues are conducting is highly unethical and unprofessional. Likewise, it would be unprofessional for a physician to recommend to a patient that she undergo an experimental protocol (outside of an IRB approved research protocol). As a physician, I would never recommend this treatment to a patient nor would I refer a patient for such care given the current state of the evidence. In the unlikely event that a patient came to me seeking not to continue the medication abortion regimen after she had ingested the mifepristone, I would initiate

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(Abortion Pill Reversal) . . . I have published a case series report in a peer-reviewed medical journal, Annals of Pharmacotherapy, and plan a second article when we have 200 deliveries.").

[71] ACOG Comm. on Ethics, *Committee Opinion No. 352: Innovative Practice: Ethical Guidelines*, 108 Obstetrics & Gynecology 1589 (2006).

[72] *Id*. at 1591.

[73] *Id*. at 1592.

comprehensive pregnancy options counseling and probe as to what had motivated the patient's change of heart; if I confirmed that she carried an ongoing pregnancy and wished to continue to term, I would then refer her for prenatal care.

Effect of the Act on the Patient-Provider Relationship

71. Even apart from the fact that the administration of progesterone to reverse, avoid, or cease the effects of mifepristone is not supported by medical evidence and that there are concerns that Dr. Delgado's research is not being conducted ethically, it is my opinion that requiring physicians to inform patients about the possibility of medication abortion reversal is in and of itself harmful to physicians and patients in a variety of ways.

72. To begin with, the vast majority of women receiving medication abortion are sure of their decision by the time they present for care at an abortion clinic,[74] so information about "reversal" would be irrelevant for those patients. Additionally, part of the value to the clinical encounter is pregnancy options counseling, when the provider reviews the plan of care with the patient *before* initiating any clinical intervention. Falsely claiming that an abortion could be reversible is dangerous to women, and dangerous to the practice of medicine. Women may erroneously believe it is advisable to start the abortion process before they are sure of their decision.

73. The Act thus disrupts and impedes the patient-provider relationship and contravenes the true purpose of the informed consent process: Namely, to give each patient medical information relevant to their healthcare decision-making in a way that is easy to absorb

[74] *See, e.g.*, Lauren J. Ralph et al., *Measuring Decisional Certainty Among Women Seeking Abortion*, 95(3) Contraception 269 (2016); Diana G. Foster et al., *Attitudes and Decision Making Among Women Seeking Abortions at One U.S. Clinic*, 44(2) Perspectives on Sexual & Reproductive Health 117 (2012).

and understand—i.e., that is clear, concise, and applicable to her circumstances and individual concerns.

74. Further, the Act requires the mandated information to be "conspicuously" posted in patient waiting rooms and consultation rooms used by patients receiving abortions, and does not limit this requirement to rooms used by patients receiving *medication* abortions. Thus, this mandated information would also be irrelevant, and even more confusing, for women who are not using mifepristone as a part of the standard medication abortion regimen, but instead are receiving drugs, such as misoprostol alone, as part of an induction or procedural abortion. No one even claims to have an effective reversal treatment in these circumstances, but that may not be clear to the patient given this confusing and irrelevant information. Moreover, a sign displaying the government's misleading message in boldfaced type, 3/4 inch (i.e. 54 point) font, as required by the Act, would be equivalent to the size of a poster. A message of this size and prominence is not typically present in a medical practice and would likely spark concern and confusion among patients. For patients seeking medication abortion with mifepristone, the notice may create confusion about whether the treatment protocol prescribed by their physician is effective, potentially eroding trust and undermining the doctor-patient relationship. The required statement on the sign and in the written discharge instructions that "[r]ecent developing research has indicated that mifepristone alone is not always effective in ending a pregnancy" is also inaccurate and misleading. The statement implies that researchers have recently discovered that mifepristone is not as effective as previously believed, which is wholly untrue—as discussed, research dating back decades showed that mifepristone failed to work sufficiently well on its own as an abortion-inducing medication, and this is precisely why the standard medication

abortion regimen involves the use of mifepristone and misoprostol in combination.[75] Ultimately, the overall effect of the notice is coercive—instilling confusion, doubt, and distrust, all in service of coercing women away from the treatment they have chosen.

75. Furthermore, the Act's requirements are confusing and misleading for medication abortion patients. Under the Act, patients must hear from their physician that reversal "may be possible," and that the Tennessee Department of Health website offers information on and assistance with obtaining this treatment. Patients must again receive the same information, from their physician or their physician's agent, after they receive mifepristone, in written medical discharge instructions. In this situation, patients are likely to conclude that this treatment is established as safe and effective, which as explained above, is far from true. In effect, the Act forces physicians and their agents to repeatedly endorse experimental medical treatment, despite the fact that the physicians do not think this treatment is in their patients' best interests. In my opinion, these problems cannot be solved by physicians providing further explanation. If a physician tried to explain that what she had just been required to tell the patient was untrue, misleading, and/or not relevant at all to the patient, that would increase patient confusion and make it harder for the physician to ensure that the patient understood all the relevant facts she needed to make an informed decision about whether or not to proceed with an abortion in the first place. It could also lead a patient not to trust any of the information the physician gave her.

76. Additionally, the Act requires physicians to give patients conflicting information, which could cause further confusion and undermine the critical physician-patient relationship of trust. The Act essentially requires physicians to tell their patients that the misoprostol is an optional part of the medication abortion two-drug combination regimen—i.e., that they can take

[75] Zheng, *supra* n.21.

mifepristone and then decide not to take misoprostol. This is at odds with other information and counseling that the FDA mandates that physicians provide to medication abortion patients. The FDA has adopted a Risk Evaluation and Mitigation Strategy ("REMS") specific to mifepristone. The REMS for mifepristone is separate from the FDA label for mifepristone; while physicians can and do prescribe evidence-based off-label uses of a drug in general, medication abortion providers must follow the FDA's REMS for mifepristone. Indeed, mifepristone manufacturers are prohibited from supplying mifepristone to healthcare providers unless they are REMS-certified.

77. The mifepristone REMS restricts who can prescribe mifepristone and how it can be provided to patients, and also mandates that certain information be provided to patients.[76] Under the mifepristone REMS, to be eligible to provide mifepristone, healthcare providers must sign a Prescriber Agreement Form agreeing that they will follow the REMS guidelines for mifepristone. Those guidelines require the provider to review the REMS-mandated Patient Agreement Form with the patient, answer any questions, and obtain the patient's signature on the form. By signing the Patient Agreement Form, the patient agrees that they will take both mifepristone and misoprostol:

> **Patient Agreement:**
>
> 1. I have decided to take Mifeprex ***and misoprostol*** to end my pregnancy and will follow my provider's advice about when to take each drug and what to do in an emergency.
>
> 2. I understand:
>
> a. I will take mifepristone on Day 1.

[76] *Risk Evaluation and Mitigation Strategy (REMS): Single Shared System for Mifepristone 200MG,* FDA (Apr. 2019), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifepristone_2019_04_11_REMS_Full.pdf.

b. My provider will either give me or prescribe for me the ***misoprostol tablets which I will take 24 to 48 hours after I take Mifeprex***.

The provider must also sign the Patient Agreement Form, confirming that he or she has counseled the patient and answered all her questions.[77]

78. Informing medication abortion patients that they should take both mifepristone and misoprostol—as providers must do under REMS—conflicts with the "reversal" message that the Act compels physicians to tell their patients.

79. Finally, I am concerned that the Act's state-mandated advisory might distort the patient's decision-making and create a risk that she would begin the abortion procedure before she was fully prepared to do so. During the informed consent discussion with my abortion patients, I stress that they should not begin the procedure until they are resolved to terminate their pregnancy.

80. If a patient shows signs of ambivalence, I advise her to reflect further, and offer her professional resources if necessary. I do this for medication abortion patients as well as procedural abortion patients because no patient should undergo a procedure or take a medication she is unsure is indicated or appropriate. In addition, with medication abortion, patients need to be emotionally prepared for the real possibility that the mifepristone *will* terminate their pregnancy (as it does in a majority of pregnancies). Taking mifepristone is the start of the abortion process.

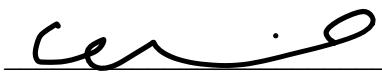
81. I believe, therefore, that introducing the misleading prospect that abortion "reversal" is possible when the patient is in the process of making their abortion decision

[77] *Patient Agreement Form,* FDA (Apr. 2019) (emphasis added), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifepristone_2019_04_11_Patient_Agreement_Form.pdf.

undermines the physician's efforts to ensure that the patient does not begin pregnancy termination treatment unless they are certain about their decision to end the pregnancy. This is contrary to the most fundamental tenets of medicine.

82. For all of these reasons, the disclosures required by the Act about mifepristone "reversal" compel physicians to distort and damage the relationship of trust that they seek to build with their patients, and forces them to provide information to their patients that they do not agree with and that they rightfully think is false, misleading, irrelevant, and/or harmful to women seeking abortions. It violates the tenets of ethical and evidence-based medical care. Rather than promoting physician autonomy in the provision of healthcare and the health of women and families, it damages the physician-patient relationship, undercuts the physician's professional integrity, and harms women.

I declare under penalty of perjury that the foregoing is true and correct.
Dated this 31 day of August, 2020.



Courtney A. Schreiber, M.D., M.P.H.

EXHIBIT A

UNIVERSITY OF PENNSYLVANIA - PERELMAN SCHOOL OF MEDICINE
Curriculum Vitae

Date: 07/26/2020

Courtney Anne Schreiber, MD, MPH

Address: Department of Obstetrics and Gynecology
3400 Spruce Street, 1000 Courtyard
Philadelphia, PA 19104 United States

If you are not a U.S. citizen or holder of a permanent visa, please indicate the type of visa you have:
none (U.S. citizen)

Education:

1993	B.A.	Columbia College, Columbia University, New York NY (Religion)
1995	OTH	University of Pennsylvania, Philadelphia, PA (Postbaccalaurate Premedical Program)
1999	M.D.	New York University School of Medicine, New York, NY
2005	M.P.H.	University of Pittsburgh, Graduate School of Public Health, Epidemiology Track, Pittsburgh, PA (Public Health)

Postgraduate Training and Fellowship Appointments:

1999-2003	Resident, Obstetrics and Gynecology, Hospital of the University of Pennsylvania, Philadelphia, PA
2003-2005	Fellow, Contraceptive Research and Family Planning, University of Pittsburgh, Dept of Obstetrics, Gynecology and Reproductive Sciences, Pittsburgh, PA

Military Service:
[none]

Faculty Appointments:

2006-2014	Assistant Professor of Obstetrics and Gynecology at the Hospital of the University of Pennsylvania, University of Pennsylvania School of Medicine
2014-2020	Associate Professor of Obstetrics and Gynecology at the Hospital of the University of Pennsylvania, University of Pennsylvania School of Medicine
2020-present	Stuart and Emily Mudd Professor of Obstetrics and Gynecology at the Hospital of the University of Pennsylvania, University of Pennsylvania School of Medicine

Hospital and/or Administrative Appointments:

2005-Present	Attending in Obstetrics and Gynecology, Hospital of the University of Pennsylvania, Department of Obstetrics and Gynecology, Philadelphia, PA

2008-2017	Founder and Director, Penn Family Planning and Pregnancy Loss Center
2009-present	Program Director, Fellowship in Family Planning, Hospital of the University of Pennsylvania
2017-present	Director, PEACE
2017-present	Division Chief, Family Planning, Department of Obstetrics and Gynecology, Penn Medicine

Other Appointments:

2018-present	Research Director, Building Interdisciplinary Research Careers in Women's Health K-12 Program, Perelman School of Medicine, University of Pennsylvania
2018-present	Senior Fellow, Leonard Davis Institute of Health Economics

Specialty Certification:

2007	American Board of Obstetrics and Gynecology

Licensure:

2003-Present	Pennsylvania Medical Licensure

Awards, Honors and Membership in Honorary Societies:

1996	Reproductive Health Fellowship, Medical Students for Choice, San Francisco, CA
1998	National Abortion Federation Early Achievement Award
1999	James E Constantine Award in Obstetrics and Gynecology, NYU School of Medicine
1999	Dr. Martin Gold Visionary Provider Award, Diana Foundation, NY, NY
2001	Resident Teaching Award, Hospital of the University of Pennsylvania
2004	Wyeth New Leader's Award Fellowship, Association of Reproductive Health Professionals
2005	Donald F. Richardson Memorial Prize Paper Award Nominee, American College of Obstetricians and Gynecologists
2005	Philip F. Williams Prize Award, American College of OB/GYN
2005	Wyeth New Leader's Award Fellowship, Association of Reproductive Health Professionals
2010	Women's Way Unsung Heroine Award: Turning Talk into Action
2011	Emily B. Hartshorne Mudd Award for Contributions to the Field of Family Health
2011	The Penn Medicine "Penn Pearls" Award for Excellence in Teaching
2015	Penn Center for Innovation Accelerator Award Phase I
2016	Penn Center for Innovation Accelerator Award Phase II

2019	Clinical Research Forum Top 10 Clinical Research Achievement Award

Memberships in Professional and Scientific Societies and Other Professional Activities:

International:

2017-present	Fellowship in Family Planning (Advisory Board (Chair, 2017-2019))

National:

1995-1999	Medical Students for Choice (Board of Directors)
1997-2002	American Medical Women's Association
1997-present	Physicians for Reproductive Choice and Health (Board of Directors 1997-1999)
1999-Present	American College of Obstetricians and Gynecologists (Physician Member, Committee on Health Care for Underserved Women (2012-13) Fellow (2002-present) Junior Fellow (1999-2008))
2001-2006	American Society for Reproductive Medicine
2003-2018	Association of Reproductive Health Professionals
2003-present	National Abortion Federation
2004-2012	American Public Health Association
2008-Present	Peer Health Exchange (Curriculum Advisory Board)
2012-present	Center for Disease Control Teen Pregnancy Prevention Project, Family Planning Council of Pennsylvania (Consultant)
2014	NIH (Study Section Reviewer: Female Contraceptive Development Program (U01))
2019-Present	American Board of Obstetrics and Gynecology, Complex Family Planning Committee (Inaugural Chair 2019)
2019-Present	The Accreditation Council for Graduate Medical Education, Complex Family Planning Task Force

Local:

2008-2016	Family Planning Council (Board Member of the Medical Committee)
2008-2016	Women's Medical Fund Medical Advisory Committee
2010-2016	American Civil Liberties Union of Pennsylvania, Clara Bell Duvall Reproductive

Freedom Project (Advisory Council Member)

2011-2017 Women's Way (Board Member. Vice Chair of the Board 2014-2016)

Editorial Positions:

2005-Present	Reviewer, Contraception
2007-Present	Reviewer, American Journal Obstetrics and Gynecology
2008-2010	Reviewer, Pharmacoepidemiology
2011-Present	Associate Editor, Contraception
2017-present	Section Editor, Contraception, UpToDate
2018-present	Section Editor, Ectopic Pregnancy, UpToDate
2018-present	Deputy Editor, Contraception

Academic and Institutional Committees:

2002-2003	House Officer Committee, Hospital of the University of Pennsylvania
2005-2010	Resident Curriculum Development Committee
2009-Present	Operating Room Committee
2010-2012	Grant Reviewer Penn CFAR Pilot Grants Program
2011-2014	Chair, Management of Early Pregnancy Failure Working Group
2012-2018	Center for AIDS Research Committee on Women and HIV
2013-2018	Core Member, Women's Health Scholar Certificate
2014-2015	Member, Department of Obstetrics and Gynecology Executive Committee
2014-present	Medical School Admissions Interview Committee, Perelman School of Medicine of the University of Pennsylvania.
2018-Present	Member, Review Committee for the Department of Biostatistics, Epidemiology, and Informatics
2018-present	Department of Obstetrics and Gynecology Executive Committee

Major Academic and Clinical Teaching Responsibilities:

2002-2003	Organizer, Ob/Gyn resident journal club, Hospital of the University of Pennsylvania
2002-Present	Lecturer, Ob/Gyn resident didactics and journal club
2005-2015	Lecture on Family Planning, Core Clinical Clerkship in Ob/Gyn (OG200), (8x/yr)
2005-2016	Faculty preceptor, Core Clinical Clerkship in Ob/Gyn (OG200), (1-2x/yr)
2006-2017	Lecturer "Contraception", Reproduction module (1 lecture/yr)
2006-2016	"Bridging the Gaps" Academic Mentor for one student each summer
2006-2017	Director, Family Planning Rotation for Ob/Gyn residents
2006-2017	Course Director, Family Planning and Abortion Care Elective (OG300), medical students
2006-2017	Small group discussion leader on abortion and contraception, Reproduction Module II (2 sessions/yr), medical students

2006-Present	Attending Physician, Family Planning, supervise and teach medical students, residents, and fellows
2006-2016	Attending physician, Resident Gynecology service (4 weeks/yr)
2006-Present	Research mentor for resident research projects
2006-2017	Lecture "Abortion," Reproduction Module II (1 lecture/yr), medical students
2006-2007	Mentor, Sabrina Sukhan, MD, Resident in Obstetrics and Gynecology "Is exposure to prenatal care associated with improved pregnancy outcomes and post-partum contraception continuation in a teenage population?"
2006	Hospital of The University of Pennsylvania Department of Obstetrics and Gynecology Grand Rounds: "The Characterization and Treatment of Early Pregnancy Failure"
2007	Division of Cardiology, University of Pennsylvania Medical Center, "Contraception in Women with Congenital Heart Disease",
2008-2010	Mentor, Monika Goyal, MD, Pediatric Emergency Fellow "Prevalence of Trichomonas vaginitis in a symptomatic adolescent ED population
2009-Present	Director, Family Planning Fellowship Program
2010-2012	Fellowship Mentor: Sara Pentlicky, MD
2010-2013	Mentor, Holly Langmuir, MD, Resident in Obstetrics and Gynecology "Immediate postpartum IUD placement: a decision analysis"
2010-2013	Mentor, Peter Vasquez, MD, Resident in Obstetrics and Gynecology "Factors that decrease morbidity among women undergoing second trimester uterine evacuation at an urban academic medical center"
2010-2013	Mentor, Ericka Gibson, MD, Resident in Obstetrics and Gynecology "Risk Factors for pregnancy during contraceptive clinical trials"
2010-2012	Mentor, Sara Pentlicky, MD, Fellow in Family Planning "Weight Loss in the postpartum: impact of different contraceptive methods"
2010-2013	Mentor, Corina Tennant, MD, Resident in Obstetrics and Gynecology "Uptake, acceptability, and continuation of the Implanon contraceptive implant immediately postpartum in an urban medical center"
2011-2013	Mentor, Lily Pemberton, MD, Resident in Obstetrics and Gynecology "establishment of an academic family planning outpatient facility increases uptake of LARC among inner-city women"
2011-2017	Public Health Perspectives in Family Planning Instructor and course co-director (offered through the MPH program)
2011-2012	Doris Duke Clinical Research Fellowship Mentor (Mentee - Kelly Quinley - Awarded Society of Academic Emergency Medicine Medical Student Excellence Award)
2011-2013	Fellowship Mentor: Stephanie Sober, MD
2011	Mentor, Valerie Colleselli, medical student, University of Innsbruck,

	Austria "Medical management of early pregnancy failure (EPF): a retrospective analysis of a combined protocol of mifepristone and misoprostol used in clinical practice"
2012-2014	Fellowship Mentor, Susan Wilson, M.D.
2012-2015	Mentor, Andrea Roe, MD, Resident in Obstetrics and Gynecology "Cystic Fibrosis and Fertility"
2012-2015	Mentor, Joni Price, MD, Resident in Obstetrics and Gynecology "Risk of unplanned pregnancy by cycle day among contracepting women"
2012-2016	Clinician Trainings for the Family Planning Council's CDC Teen Pregnancy Prevention Project
2014-2015	Mentor, Pooja Mehta, MD, ACOG Industry-Funded Research Fellowship in Contraceptive Access within Low-Resource Populations
2014-2016	Mentor, Elizabeth Gurney, MD, Fellow in Family Planning "Six-month Retention Rates of Copper IUDs Placed Immediately Post-placentally"
2014-2016	Mentor, Alyssa Colwill, MD, Resident in Obstetrics and Gynecology "Immediate Post-placental IUD Expulsion - a Retrospective Cohort Study"
2015	"Prevention and Management of Early Pregnancy Complications," Department of Obstetrics and Gynecology, Pennsylvania Hospital, Philadelphia PA
2015-2017	Mentor, Elizabeth Greenstein, MD, Resident in Obstetrics and Gynecology "Doctor-Patient Communication at the Time of Miscarriage Management"
2015-2018	Mentor, Maryl Sackheim, MD, Resident in Obstetrics and Gynecology: "Rapid Repeat Pregnancy at Penn Medicine: Prevalence and Risk Factors"
2015-2017	Mentor, Alhambra Frarey, MD, Fellow in Family Planning "Referral and Delay in Abortion Care: a Cross-sectional Study"
2015	"Contraception for women with rheumatologic disease," Division of Rheumatology of Penn Medicine, Philadelphia Pa.
2016-2018	Mentor, Sarah Horvath, MD, Fellow in Family Planning "Quantifying Feto-Maternal Hemorrhage in the First Trimester of Pregnancy"
	Winner, Society of Family Planning Young Investigator Award, 2018
2016	"History of Contraception in the US," Master of Public Health Program, University of Pennsylvania, Philadelphia PA
2016	"Academic Medicine as an Instrument of Change," Master of Science of Health Policy, University of Pennsylvania, Philadelphia PA
2017	"The role of public health practice and research in reproductive health" Master of Public Health Program, University of

	Pennsylvania Perelman School of Medicine. Philadelphia, PA
2017-2019	Mentor, Divyah Nagendra, MD, Fellow in Family Planning "Pain Control for Uterine Evacuation: a Non-Inferiority Trial"
2017	"Academic Medicine as an Instrument of Change," University of Pennsylvania MSHP Program
2018	Pediatric Grand Rounds: Children's Hospital of Philadelphia, "Progress and Opportunities in Adolescent Reproductive Health"
2018-2020	Mentor, Jade Shorter, MD, Fellow in Family Planning "Disparities in Reproductive Health: The Patient Experience with Miscarriage Management"

Lectures by Invitation (Last 5 years):

Apr, 2015	"Prevention and Management of Early Pregnancy Complications," Department of Obstetrics and Gynecology of Jefferson Hospital, Philadelphia PA
Jul, 2015	"Immediate Postpartum Long Acting Reversible Contraception." Philadelphia Board of Health, Department of Health
Mar, 2016	"Increasing Access to Long-Acting Reversible Contraception for Philadelphia Women." Public Health and Preventive Medicine Section at the College of Physicians of Philadelphia, PA
Apr, 2016	Liletta: Challenges and Advantages of a New LNG IUD. Moderated a webinar for the Fellowship in Family Planning and Ryan Program Nationally
Apr, 2016	"Immediate Postpartum LARC: Evidence and Implementation." Department of Obstetrics & Gynecology Grand Rounds. WellSpan / York Hospital, York PA
Oct, 2016	"Unpacking Complex Contraception," University of British Columbia Interdisciplinary Grand Rounds, Vancouver, BC
Dec, 2016	"LARC for the medically complex patient," ACOG LARC Program, CME accredited webinar
Oct, 2017	"Climbing the career ladder and lifting others as you climb." Society for Family Planning Career Development Seminar, Atlanta, GA.
Nov, 2017	"Pregnancy of Unknown Location" Early Pregnancy Symposium. Philadelphia, PA
Nov, 2017	"Personalized Approaches to Early Pregnancy Loss Care" Early Pregnancy Symposium. Philadelphia, PA
Jan, 2018	"Patient-Centered Early Pregnancy Loss Care," UC San Diego Obstetrics and Gynecology Grand Rounds, San Diego, CA
Apr, 2018	"Hormonal Contraception and the Risk of Mood Symptoms," North American Society for Psychosocial Obstetrics and Gynecology, Philadelphia, PA.
Oct, 2018	"Advances in the Care of Patients with Early Pregnancy Loss," Magee-Women's Hospital Alumni Day, Pittsburgh, PA
Nov, 2018	"Healthy Child-Spacing, Healthy Families: Best Practices in Postpartum Contraception" Plenary session, Chilean Society of Obstetrics and Gynecology (SOCHOG) and the Chilean Section of

	ACOG, Santiago, Chile
Nov, 2018	"Miscarriage Management: Updates and Innovations" Plenary session, Chilean Society of Obstetrics and Gynecology (SOCHOG) and the Chilean Section of ACOG, Santiago, Chile
Nov, 2018	"Advances is Early Pregnancy Loss Care" Einstein Healthcare Network, Obstetrics and Gynecology Departmental Grand Rounds
Jan, 2019	"Advances in the Care of Patients with Early Pregnancy Loss," Obstetrics and Gynecology Grand Rounds, MedStar Washington Hospital Center and MedStar Georgetown University Hospital, Washington, D.C.
Mar, 2019	"Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss" Ob/Gyn Grand rounds, Beth Israel Deaconess Medical Center, Boston MA
Mar, 2019	"The Medical Management of Early Pregnancy Loss," Translational Science 2019 Conference, Washington, DC
Jul, 2019	"Abortion in the United States," Department of Obstetrics and Gynecology University of Helsinki, Helsinki, Finland.
Jul, 2019	"Biomarkers of Human Reproduction," Department of Obstetrics and Gynecology, Karolinska Institute, Stockholm, Sweden.
Jan, 2020	"Advances in the Care of Patients with Early Pregnancy Loss," Columbia University Medical Center Obstetrics and Gynecology Grand Rounds, New York, NY.

Organizing Roles in Scientific Meetings:

Apr, 2010	Chair, National Abortion Federation 2010 Postgraduate course: "Team Work and Patient Safety" Philadelphia, PA
2011	Co-Chair HIV and Women subgroup of the Penn Center For Aids Research Philadelphia, PA
Apr, 2013	Facilitator: Controversies in Family Planning. Fellowship in Family Planning Annual Meeting Chicago, IL
May, 2013	Co-Chair, Penn CFAR Women and HIV Symposium: "Biobehavioral approaches to HIV prevention and management in adolescent women" Perelman School of Medicine, Philadelphia PA
May, 2013	Facilitator: Controversies in Family Planning. Fellowship in Family Planning Annual Meeting Denver, CO
May, 2014	Facilitator: Controversies in Family Planning. Fellowship in Family Planning Annual Meeting New Orleans, LA
Apr, 2015	Moderator, second year family planning fellows' research presentations on contraception San Francisco, California

Apr, 2017	Organizer and Panel Moderator, "Moving Forward: Protecting and Promoting Reproductive Health" University of Pennsylvania
May, 2019	Chairperson, Directors' Meeting, Fellowship in Family Planning Boston, Mass

Bibliography:

Research Publications, peer reviewed (print or other media):

1. Schreiber CA, Wan L, Sun Y, Krey L, Lee-Huang S: The antiviral agents MAP30 and GAP31 are not toxic to human spermatozoa and may be useful in preventing the sexual transmission of HIV-I. Fertil Steril 72:686-690, 1999.

2. Murthy AS, Creinin MD, Harwood BJ, Schreiber CA: Same day initiation of the transdermal hormonal delivery system (contraceptive patch) versus traditional initiation methods. Contraception 72(5):333-36, 2005.

3. Murthy AS, Creinin MD, Harwood BJ, Schreiber CA: A pilot study of mifepristone and misoprostol administered at the same time for abortion up to 49 days gestation. Contraception 71(5):333-336, 2005.

4. Schreiber CA, Creinin MD, Harwood BJ, Murthy AS: A pilot study of mifepristone and misoprostol administered at the same time for abortion from 50-63 days gestation. Contraception 71(6):447-50, 2005.

5. Schreiber CA, Creinin MD, Reeves MF, Harwood BJ: Mifepristone and misoprostol for the treatment of early pregnancy failure: a pilot clinical trial. Contraception 74:458-462, 2006.

6. Schreiber CA, Harwood BJ, Switzer GE, Creinin MD, Reeves MF, Ness RB: Training and attitudes about contraceptive management across primary care specialties: a survey of graduating residents. Contraception 73:618-622, 2006.

7. Schreiber CA, Meyn, L, Creinin MD, Barnhart KT, Hillier SL: The effects of long-term use of nonoxynol-9 on vaginal flora. Obstet Gynecol 107:1-9, 2006.

8. Creinin MD, Schreiber CA, Bednarek P, Lintu H, Wagner MS, Meyn LA: Medical abortion at the same time (MAST) study trial group. Mifepristone and misoprostol administered simultaneously versus 24 hours apart for abortion: a randomized controlled trial. Obstet Gynecol 109(4):885-894, 2007.

9. Schreiber CA, Sammel M, Barnhart KT, Hillier SL: A little bit pregnant: Modeling how the accurate detection of pregnancy can improve HIV prevention trials. Am J Epidemiol 169(4):515-521, 2009.

10. Schreiber CA, Ratcliffe SJ, Barnhart KT: A randomized controlled trial of the effect of advanced supply of emergency contraception in postpartum teens: a feasibility

study. Contraception 81(5):435-40, 2010.

11. Schreiber CA, Sober S, Ratcliffe S, Creinin MD: Ovulation resumption after medical abortion with mifepristone and misoprostol. Contraception 84(3):230-3, 2011.

12. Schreiber CA, Whittington S, Cen L, Maslankowski, L: Good Intentions: Risk factors for unintended pregnancies in the U.S. cohort of a microbicide trial. Contraception 83(1):74-81, 2011.

13. Su IH, Schreiber CA, Fay C, Parry S, Elovitz MA, Zhang J, Shaunik A, Barnhart K: Mucosal integrity and inflammatory markers in the female lower genital tract as potential screening tools for vaginal microbicides. Contraception 84(5):525-32, 2011.

14. Chen SP, Massaro-Giordano G, Pistilli M, Schreiber CA, Bunya V: Tear osmolarity and dry eye symptoms in women using oral contraception and contact lenses. Cornea 32(4):423-8, 2013.

15. Kinariwala M, Quinley K, Datner E, Schreiber CA: Manual vacuum aspiration in the emergency department for management of early pregnancy failure. Am J Emerg Med 31(1):244-7, 2013.

16. Pentlicky S, Rosen M, Coffey P, Kilbourne-Brook M, Shaunik A, Schreiber CA, Barnhart K: An exploratory, randomized, crossover MRI study of microbicide delivery with the SILCS diaphragm compared to a vaginal applicator. Contraception 87(2):187-92, 2013.

17. Swica Y, Chong E, Middleton T, Prine L, Gold M, Schreiber CA, Winikoff B: Acceptability of home use of mifepristone for medical abortion. Contraception 88(1):122-7, 2013.

18. Colleselli V, Schreiber CA, D'Costa E, Mangesius S, Ludwig W, Seeber BE: Medical management of early pregnancy failure (EPF):a retrospective analysis of a combined protocol of mifepristone and misoprostol used in clinical practice. Arch Gynecol Obstet 289(6): 1341-45, Jun 2014.

19. Foster DG, Grossman D. Turok DK, Peipert JF, Prine L, Schreiber CA, Jackson A, Barar R, Schwarz EB: Interest in and experience with IUD self-removal. Contraception 90(1): 54-59, Jul 2014.

20. Wilson S, Tennant C, Sammel MD, Schreiber C: Immediate postpartum etonogestrel implant: a contraception option with long-term continuation. Contraception 90(3): 259-64, Sep 2014.

21. Quinley K, Ratcliffe S, Schreiber C: Psychological coping in the immediate post-abortion period. J Women's Health 23(1):44-50, 2014.

22. Schreiber CA, Traxler S: State of family planning. Clin Obstet Gynecol 58(2): 392-408, Jun 2015

23. Eisenberg DL, Schreiber CA, Turok DK, Teal SB, Westhoff CL, Creinin MD: Three-year efficacy and safety of a new 52-mg levonorgestrel-releasing intrauterine system. Contraception 92(1): 10-16, Jul 2015.

24. Quinley KE, Falk A, Kallan MJ, Datner EM, Carr BG, Schreiber CA: Validation of ICD-9 Codes for Stable Miscarriage in the Emergency Department. West J Emerg Med 16(4): 551-6, Jul 2015.

25. Schreiber CA, Ratcliffe SJ, Quinley KE, Miller C, Sammel MD: Serum biomarkers to predict successful misoprostol management of early pregnancy failure. Reprod Biol 15(2): 79-85, 2015.

26. Schreiber CA, Ratcliffe SJ, Sammel MD, Whittaker PG.: A self-assessment efficacy tool for spermicide contraceptive users. Am J Obstet Gynecol 214(2): 264.e1-7, Feb 2016.

27. Sober S, Shea J, Shaber A, Whittaker P, Schreiber C: Postpartum Adolescents' Contraceptive Counselling Preferences. Eur J Contracept Reprod Health Care 22(2): 83-87, April 2016.

28. Wilson SF, Degaiffier N, Ratcliffe SJ, Schreiber CA: Peer counselling for the promotion of long-acting, reversible contraception among teens: a randomised, controlled trial. Eur J Contracept Reprod Health Care 21(5): 380-7, Oct 2016.

29. Roe AH, Traxler SA, Hadjiliadis D, Sammel MD, Schreiber CA: Contraceptive choices and preferences in a cohort of women with cystic fibrosis. Respir Med 121: 1-3, Dec 2016.

30. Schreiber CA, Chavez V, Whittaker PG, Ratcliffe SJ, Easley E, Barg FK: Treatment Decisions at the Time of Miscarriage Diagnosis. Obstet Gynecol 128(6): 1347-1356, Dec 2016.

31. Frisse AC, Marrazzo JM, Tutlam NT, Schreiber CA, Teal SB, Turok DK, Peipert JF: Validity of Self-Reported History of Chlamydia trachomatis Infection. Am J Obstet Gynecol 216(4): e1-393, April 2017.

32. Akers AY, Steinway C, Sonalkar S, Perriera LK, Schreiber C, Harding J, Garcia-Espana JF: Reducing Pain During Intrauterine Device Insertion: A Randomized Controlled Trial in Adolescents and Young Women. Obstet Gynecol 130(4): 795-802, Oct 2017.

33. Sonalkar S, Gurney EP, McAllister A, Schreiber CA: A randomized pilot evaluation

of individual-level abortion stigma resulting from Pennsylvania mandated abortion counseling. Contraception 96(4): 227-232, Oct 2017.

34. Colwill AC, Schreiber CA, Sammel MD, Sonalkar S: Six-week retention after postplacental copper intrauterine device placement. Contraception 97(3): 215-218, Mar 2018.

35. Schreiber CA, Teal SB, Blumenthal PD, Keder LM, Olariu AI, Creinin MD: Bleeding patterns for the Liletta levonorgestrel 52 mg intrauterine system. Eur J Contracept Reprod Health Care 23(2): 116-120, Apr 2018.

36. Akers AY, Harding J, Perriera LK, Schreiber CA, Garcia-Espana JF, Sonalkar S: Satisfaction with the Intrauterine Device Insertion Procedure Among Adolescent and Young Adult Women. Obstet Gynecol 131(6): 1130-1136, Jun 2018.

37. Schreiber CA, Creinin MD, Atrio J, Sonalkar S, Ratcliffe SJ, Barnhart KT: Mifepristone pretreatment for the medical management of early pregnancy loss. N Engl J Med 378(23): 2161-70, Jun 2018 Notes: selected as a CME activity for the New England Journal of Medicine.

38. Gurney EP, Sonalkar S, Mcallister A, Sammel MD, Schreiber CA: Six-month expulsion of postplacental copper intrauterine devices placed after vaginal delivery. Am J Obstet Gynecol 219(2): 183.e1-183.e9, Aug 2018.

39. Whittaker PG, Schreiber CA, Sammel MD: Gestational hormone trajectories and early pregnancy failure: a reassessment. Reprod Biol Endocrinol 16(1): 95, Oct 2018.

40. Sonalkar S, Hunter T, Gurney EP, McAllister A, Schreiber CA: A Decision Analysis Model of 1-Year Effectiveness of Intended Postplacental Compared with Intended Delayed Postpartum Intrauterine Device Insertion. Obstet Gynecol 132(5):1211-122, Nov 2018.

41. Clement EG, Horvath S, McAllister A, Koelper NC, Sammel MD, Schreiber CA: The Language of First-Trimester Nonviable Pregnancy: Patient-Reported Preferences and Clarity. Obstet Gynecol 133(1):149-154, Jan 2019.

42. Frarey A, Gurney EP, Sober S, Whittaker PG, Schreiber CA: Postpartum contraceptive counseling for first-time adolescent mothers: a randomized controlled trial. Arch Gynecol Obstet 299(2):361-369, Feb 2019.

43. Frarey A, Schreiber C, McAllister A, Shaber A, Sonalkar S, Sammel MD, Long jA: Pathways to Abortion at a Tertiary Care Hospital: Examining Obesity and Delays. Perspect Sex Reprod Health 51(1):35-41, Mar 2019.

44. Sackeim MG, Gurney EP, Koelper N, Sammel MD, Schreiber CA: Effect of

contraceptive choice on rapid repeat pregnancy. Contraception 99(3):184-186, Mar 2019.

45. Chen BA, Blithe DL, Muraguri GR, Lance AA, Carr BR, Jensen JT, Kimble TD, Murthy AS, Schreiber CA, Thomas MA, Walsh TL, Westhoff C, Burke AE: Acceptability of the Woman's Condom in a phase III multicenter open-label study. Contraception 99(6): 357-362, Jun 2019.

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EXHIBIT B

Progesterone Use to Reverse the Effects of Mifepristone

George Delgado and Mary L Davenport

OBJECTIVE: To present a series of cases demonstrating successful reversal of mifepristone effects in women who chose to reverse the medical abortion process.

CASE REPORTS: Four of 6 women who took mifepristone were able to carry their pregnancies to term after receiving intramuscular progesterone 200 mg.

DISCUSSION: Mifepristone has been available in the US since 2000. By 2008, approximately 25% of abortions prior to 9 weeks were accomplished with mifepristone. Some women who take mifepristone wish to reverse the medical abortion process. Progesterone competes with mifepristone for the progesterone receptor and may reverse the effects of mifepristone. A PubMed literature search from 1996 to May 2012 did not reveal any trials or case studies evaluating the efficacy of progesterone use to reverse the effects of mifepristone.

CONCLUSIONS: Health care professionals should be aware of the possible use of progesterone to reverse mifepristone in women who have begun the medical abortion process by taking mifepristone and then change their minds.

KEY WORDS: medical abortion, mifepristone, progesterone.

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Mifepristone has been available in the US as an oral tablet since 2000. It is indicated by the Food and Drug Administration (FDA) for termination of pregnancy up to 49 days after the first day of the last menstrual period. Mifepristone is followed 2 days later by misoprostol to complete the abortion.[1]

The drug's development was hailed as a breakthrough in abortion technology and as an advance for women in facilitating control of their bodies and privacy. By 2008, medical abortion replaced surgical abortion in one-fourth of approximately 800,000 abortions performed annually prior to 9 weeks.[2]

We present a series of patients who took mifepristone to terminate their pregnancies and then sought assistance to block the mifepristone effects. The 2-day gap between the ingestion of mifepristone and misoprostol in the typical abortion regimen potentially affords an opportunity to intervene and reverse the effects of the mifepristone. Six physicians in the US trained in NaProTECHNOLOGY protocols at the Pope Paul VI Institute have given progesterone as an antidote to mifepristone, treating 7 patients. The rationale of the proposed treatment was that higher bioavailable levels of progesterone could competitively inhibit the mifepristone to prevent the induced abortion.

Pharmacology of Mifepristone and Progesterone

Mifepristone was first tested to take advantage of its anti-glucocorticoid properties. It binds with high affinity to glucocorticoid receptors, about 4 times as avidly as dexamethasone.[3] When its antiprogesterone properties were discovered it was considered useful for fertility control because of its potential to counteract the actions of progesterone, which is critical for sustaining pregnancy.[4] Additionally, it has been studied for the treatment of endometriosis, uterine fibroids, and Cushing syndrome.[5-7] Mifepristone's most significant application has been in induced abortion because, by binding to the progesterone receptor, placental failure ensues and the developing embryo loses its nutrition and oxygen supply.

Mifepristone is an orally active compound with a nearly 70% absorption rate, but its bioavailability is reduced to approximately 40% because of the first-pass effect.[8] It binds to the progesterone receptor twice as well as progesterone, in addition to binding to the serum transport protein α_1-acid glycoprotein.[9] Demethylation and hydroxylation are catalyzed by CYP3A4; 3 metabolites retain biologic activity. The half-life of mifepristone is approximately 18-25 hours. Mifepris-

Author information provided at end of text.

tone and its metabolites can be measured up to 72 hours after an ingested dose.[10] The half-life of progesterone is longer, approximately 25-55.13 hours.[11-13]

Current Regimens of Medical Abortion

The original FDA-approved regimen of mifepristone and misoprostol paralleled the European protocol that had been used in the 1990s. It consisted of mifepristone 600 mg followed 2 days later by oral misoprostol 400 µg.[14] Later trials evaluated mifepristone 200 mg.[15-18] The FDA and the drug's distributor recommend the 600-mg dose; however, others state that the 200-mg dose has been used in most of 1 million abortions.[19] The success rate of medical abortion decreases with gestational age. In the FDA clinical trials the rate of incomplete abortion was 5% before 49 days and 7-8% at 50-63 days; the rate of an ongoing living embryo ranged from less than 1% before 49 days to 9% at 57-63 days.[14]

Results of Progesterone Therapy

We report on 6 women who were treated with progesterone in an attempt to reverse pregnancy termination after mifepristone ingestion. Four of these women eventually delivered healthy term newborns. A seventh patient was lost to follow-up. Of the 2 abortions, 1 occurred soon after an intramuscular injection of progesterone was administered (patient 6). Data on this patient are incomplete. The other patient (patient 5) received progesterone micronized 200 mg vaginally 7 hours after ingesting mifepristone and receiving progesterone 200 mg intramuscularly 18 hours after mifepristone. However, a live embryo was not documented at the abortion clinic or in the physician's office for this patient.

Case Reports

CASE 1

A 19-year-old woman, gravida (G) 1 para (P) 0, elected to have the mifepristone effects reversed at gestation age 8 weeks. Misoprostol had not been ingested. The initial progesterone dose was 200 mg in oil intramuscularly 30-40 hours following mifepristone ingestion. The progesterone regimen was given 2 consecutive days and then 2 doses every other day, and then twice a week until 9 weeks 5 days.

Progesterone 200 mg in oil intramuscularly was restarted at 11 weeks 2 days and given twice weekly; the dose was then decreased to 100 mg twice a week and stopped at 29 weeks 5 days.

A viable male was delivered at 37 weeks. No untoward effects of progesterone noted and no birth defects were noted. Neonatal complications included neonatal physiologic jaundice and circumcision wound infection.

CASE 2

A 25-year-old woman, G8 P7007, elected to have the mifepristone effects reversed at gestation age 11 weeks. Misoprostol had not been ingested. The initial progesterone dose was 200 mg in oil intramuscularly 72 hours following mifepristone ingestion.

Further progesterone treatment included an intramuscular injection of 200 mg in oil for 2 weeks, then progesterone micronized orally for 5 months. No untoward effects of progesterone were noted.

A viable infant was delivered, with no neonatal complications or birth defects noted.

CASE 3

A 19-year-old woman, G3 P1011, elected to have the mifepristone effects reversed at gestation age 7 weeks. Misoprostol had not been ingested. The initial progesterone dose was 200 mg in oil intramuscularly 36-48 hours following mifepristone ingestion.

Further progesterone treatment included an intramuscular injection of 200 mg in oil 2 more times the first week, then weekly for 5-6 weeks, then 200 mg in oil twice weekly for 2 weeks, then micronized progesterone orally for 5 months. No untoward effects of progesterone were noted.

A viable infant was delivered at 39 weeks 3 days, with no neonatal complications or birth defects noted.

CASE 4

A 20-year-old woman, G1 P0, elected to have the mifepristone effects reversed at gestational age 7 weeks 4 days. Misoprostol had not been ingested. The initial progesterone dose was 200 mg in oil intramuscularly 46 hours following mifepristone ingestion. Further progesterone treatment included an intramuscular injection of 200 mg in oil twice weekly for 19 weeks. No untoward effects of progesterone were noted.

A viable female infant was delivered at 40 weeks 1 day, with no neonatal complications or birth defects noted.

CASE 5

A 21-year-old woman elected to have the mifepristone effects reversed; gestational age was unknown. Misoprostol had not been ingested. The initial progesterone dose was 200 mg in oil (time following mifepristone ingestion unknown). The abortion was completed soon after the progesterone injection.

CASE 6

A 19-year-old woman, G1 P0, elected to have the mifepristone effects reversed at gestational age 7 weeks. Misoprostol had not been ingested. The initial micronized

progesterone oral capsule dose was 200 mg administered intravaginally 7 hours following mifepristone ingestion. Further progesterone treatment included an intramuscular injection of 200 mg 18 hours after ingestion, which was repeated 2 days later. No untoward effects of progesterone were noted.

The abortion was completed 3 days after mifepristone ingestion.

Discussion

The experience of these patients suggests that medical abortion can be arrested by progesterone injection after mifepristone ingestion prior to misoprostol due to the competitive action of progesterone versus mifepristone. Possible confounding factors are the lack of embryocidal and feticidal efficacy of mifepristone with increasing gestational age and the absence of documentation of viable pregnancy before ingestion of mifepristone in some patients. We welcome further clinical trials utilizing this protocol or others, in order to have an evidence basis for the best protocol. We believe that if further trials confirm the success without complications of this or similar protocols, it should become the standard of care for obstetrician-gynecologists, family physicians, and emergency department physicians to attempt mifepristone reversal on patient request.

SUGGESTED PROTOCOL

A rational protocol for treating women who have ingested mifepristone and then wish to continue the pregnancy can be considered. We drew on our experience of successfully treating pregnant women with threatened spontaneous abortion or low serum progesterone levels with intramuscular progesterone using the protocol of Hilgers.[19,20] Progesterone has been studied extensively and appears to be safe during all trimesters of pregnancy.

Table 1. Progesterone Dosing and Ultrasound Time Table[a]

Day	Progesterone 200 mg Intramuscularly	Ultrasound to Confirm Viability
1	X	X
2	X	
3	X	
5	X	
7	X	X
9	X	
11	X	
13	X	X
16[a]	X	

[a]Continue twice per week until the end of the first trimester. At end of the first trimester, the dose should be tapered according to the protocol of Hilgers.[19,20]

Protocol

1. Progesterone 200 mg intramuscularly as soon as possible after ingestion of mifepristone.
2. Transvaginal or transabdominal ultrasound as soon as possible to confirm embryonic or fetal viability (Table 1). If less than 6.5 weeks after last menstrual period, monitor serial human chorionic gonadotropin (HCG) levels. However, HCG levels may not increase at the same rate as those of healthy controls.
3. Repeat progesterone 200 mg intramuscularly daily for 2 more days, then every other day until day 13 after the ingestion of mifepristone.
4. Treat with progesterone 200 mg intramuscularly twice weekly until the end of the first trimester and according to the protocol of Hilgers.[19,20] However, do not decrease the dose until the end of the first trimester.

A primary care physician or emergency medicine physician may not want to continue the protocol once it is initiated. Such physicians may want to be ready to refer the patient to a physician comfortable with progesterone supplementation during pregnancy.

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Conflict of interest: Authors reported none

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EXHIBIT C

A Case Series Detailing the Successful Reversal of the Effects of Mifepristone Using Progesterone

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ABSTRACT:

Background: Some women who take mifepristone, a progesterone receptor antagonist, in order to terminate their pregnancies, change their minds and desire to stop the medical abortion process. There are only two articles in the medical literature documenting the reversal of the effects of mifepristone.

Objective: We present and analyze a series of women who attempted to reverse the effects of mifepristone by taking supplemental progesterone to determine if the reversal of the effects mifepristone with progesterone is possible and safe. Additionally, we compare different progesterone regimens to determine relative efficacies.

Methods: This is a retrospective analysis of clinical data of 754 patients who decided to attempt to reverse the medical abortion process after taking mifepristone but before taking the second drug in the protocol, misoprostol. We followed the patients, who were given progesterone in an effort to reverse

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the effects of mifepristone, and conducted statistical analyses to determine the efficacies of different protocols compared to a control mifepristone embryo survival rate, derived from the literature.
***Results*: Intramuscular progesterone and high dose oral progesterone were the most effective with reversal rates of 64% ($P < 0.001$) and 68% ($P < 0.001$), respectively. There was no apparent increased risk of birth defects.**
***Conclusions*: The reversal of the effects of mifepristone using progesterone is safe and effective.**

Introduction

Medical induced abortion utilizing mifepristone has been available in the United States since 2000. In 2014, 31% of non-hospital induced abortions were medical induced abortions.[1] Some women decide to attempt to reverse the medical abortion process after taking mifepristone but before taking misoprostol, and inquire about the possibility of reversing the effects of mifepristone.[2]

The new FDA protocol, approved for medical abortion in 2016, involves the administration of mifepristone 200 mg orally as a single dose, which leads to embryonic or fetal demise, followed 24-48 hours later by misoprostol 800 mcg buccally as a single dose, which stimulates myometrial contractions. The protocol is approved up to 70 days after the first day of the last menstrual period.[3] Misoprostol is part of the protocol because mifepristone alone has an incomplete abortion rate of 20-40%, as determined by the end point of complete expulsion.[4]

Pharmacology

Mifepristone is a competitive antagonist of progesterone at the progesterone receptor (PR). It binds to the PR twice as avidly as progesterone.[5] Mifepristone is an orally active compound with a nearly 70% absorption rate, but its bioavailability is reduced to approximately 40% because of the first-pass effect.[6]

Demethylation and hydroxylation are catalyzed by CYP3A4; three metabolites retain biologic activity. The half-life of mifepristone is approximately 18-25 hours. Mifepristone and its metabolites can be measured up to 72 hours after an ingested dose.[5] The half-life of progesterone is longer, approximately 25-55 hours.[6,7]

Effects of Mifepristone

By blocking progesterone receptors, mifepristone leads to the separation of the decidua basalis from the trophoblast. This separation diminishes the oxygen and nutrients that can be delivered to the embryo or fetus by the maternal circulation and is the primary embryocidal and feticidal effect of mifepristone.[4,8,9]

In addition to this primary effect, mifepristone causes softening and dilatation of the cervix.[4] It also leads to myometrial contractions, increased myometrial sensitivity to prostaglandins[4,10] and the disinhibition of prostaglandin synthesis by the myometrium.[11]

Progesterone has been shown to have an autoregulatory effect on progesterone synthesis by the corpus luteum. Blocking progesterone receptors with mifepristone decreases progesterone secretion by the corpus luteum.[12]

Logic of Using Progesterone to Reverse Mifepristone Effects

Mifepristone is a competitive inhibitor of the progesterone receptor. It is well known that receptor agonism and antagonism are parts of a dynamic process that can be influenced by changing concentrations of the agonist or antagonist. Therefore, it makes biologic sense that increasing the progesterone levels in a pregnant woman by giving supplemental progesterone would favor the agonist progesterone effects and blunt the abortifacient effects of mifepristone.

An Animal Model

A Japanese rat study provides basic-science evidence of the ability of progesterone to negate the effects of mifepristone. In this experiment, one group of pregnant rats was given mifepristone while a second was given mifepristone and progesterone. In the group that only received mifepristone, only 33% of the pups survived. In the group that received mifepristone and progesterone, 100% of the pups survived. Furthermore, the first group had characteristic changes in the myometrium and ovaries; the group that received the combination had no such changes.[13]

Early Mifepristone Studies Reporting Continuing Pregnancy

When mifepristone was first studied as an abortifacient, misoprostol was not part of the protocol. During the 1980's, researchers determined that even though mifepristone was effective as an abortifacient, they believed it was necessary to add a prostaglandin analog to achieve a satisfactory complete uterine evacuation rate.[4] We must emphasize that the definition of incomplete abortion is incomplete emptying of the uterus.[14] Embryo or fetus survival is not implied.

The earliest studies also revealed that some embryos survived mifepristone. Baulieu, the principal developer of the drug, stated that at 4-7 weeks the percentages of efficacy of the regimen were approximately 70% for complete abortions, 20% for incomplete abortions and 10% for ongoing pregnancies (i.e., presumed embryo survival). For gestations 8-10 weeks, the comparable rates were 50% for complete abortions, 35% for incomplete abortions and 15% for embryo survival.[15]

In 2015, Grossman et al. published a review of the first case series of progesterone reversal of mifepristone, as well as 13 studies from the 1980's, addressing continuing pregnancies after mifepristone. The authors concluded that there was insufficient evidence to show that progesterone therapy improved survival over expectant management, based on the reported high ongoing pregnancy rates in some of these older studies.[16] However, closer scrutiny of the studies cited for high ongoing pregnancy rates reveals inadequate criteria for the diagnosis of continuing pregnancies. Many early researchers focused on an efficacy end point of complete uterine evacuation, and did not distinguish missed or incomplete abortions from continuing pregnancies (embryo or fetus

survival).[17] Only eight studies cited by Grossman had criteria sufficient to determine embryo survival and showed continuing pregnancy rates of 8-25%.[17]

A recent review found that 18 of the 30 articles investigating mifepristone monotherapy had adequate criteria to determine embryo survival.[17] After eliminating duplicate publications, 12 studies were identified which utilized follow-up ultrasound to distinguish between incomplete or missed abortion and embryo survival at the end of the study period. The mean percentage of embryos surviving mifepristone among all studies was 12.6%.[17] A single dose of 600 mg in five studies of early gestations 42-49 days in 493 subjects showed survivals of 9.4-17.1%.[17,18,19,20,21] Three studies of 58 women with gestations <49 days, using the current predominant 200-300 mg doses, noted embryo survival rates of 10-23.3%.[19,22,23,24] Four studies of 83 women included gestations up to 70 days, daily doses of 100-200 mg, and total doses 400-800 mg.; in three of these four studies, embryo survival was <25%.[25,26,27,28,29,30,31]

Methods

This is a retrospective analysis of clinical data of a group of pregnant women who took progesterone in an effort to reverse the effects of mifepristone. The study was reviewed and approved by an institutional review board. The lead author contributed clinical data from a variety of clinical settings across the United States and several other countries for comparison.

Subjects were pregnant women who had taken mifepristone, but had not yet taken misoprostol, and were interested in reversing its effects. Subjects called an informational hotline linked to an informational website and staffed by nurses and a physician assistant. After receiving information about the reversal process, those who decided to proceed with reversal were referred to physicians and mid-level practitioners in their respective geographic areas for treatment. The women gave written informed consent for treatment to their respective treating medical professionals that included permission to track their data. Data were collected from the women themselves and from their treating healtcare professionals.

Data were collected for different variables including gestational age at the time of mifepristone ingestion, mode of delivery of progesterone given, amounts of progesterone received, birth defects and preterm delivery. Progesterone was given in a variety of regimens by the 325 different medical professionals who treated these women. The modes of delivery of progesterone were intramuscular injection of progesterone in oil, oral administration of micronized progesterone, vaginal use of oral micronized progesterone capsules, compounded micronized progesterone vaginal suppositories, progesterone vaginal gel and progesterone vaginal suppositories.

We selected a 25% embryo or fetus survival rate, if mifepristone alone is administered, as a control because it is at the upper range of mifepristone survival rates and close to the 23% survival rate of the one early study that used a single 200 mg dose, the dose currently favored for medical abortions.[17] This study is designed to ascertain which progesterone treatments clinicians have offered to women seeking mifepristone

reversal that demonstrate efficacy beyond the 25% embryo survival rate, and compares the relative efficacies of different treatment protocols to the historic control.

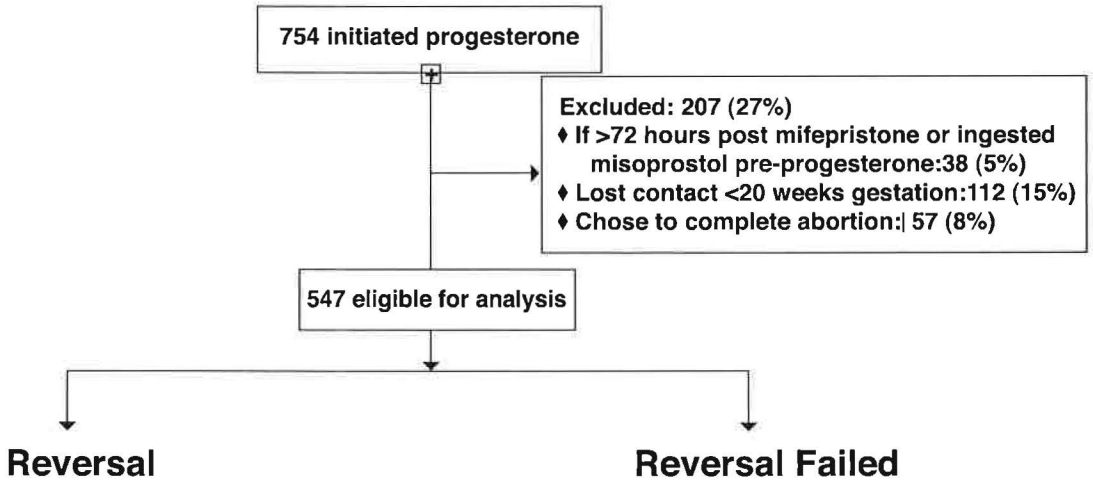
Results

From June 24, 2012 to June 21, 2016, 1,668 calls were received by the hotline from women who had taken mifepristone and were interested in reversal. Seven hundred fifty-four (45%) actually initiated progesterone therapy.

Subjects were included in the study if they were 72 hours or less post-mifepristone and had not taken misoprostol; 38 (5%) did not meet these criteria. Of the women who started progesterone therapy and met inclusion criteria, 116 (15.4%) were lost to follow-up at some point. Of those,112 (14.9%) were lost to follow-up prior to 20 weeks gestation and were excluded from the analysis. Four (0.5%) women remained pregnant with viable fetuses but were lost to follow-up after twenty weeks gestation and were included in the analysis as reversals.

Fifty-seven (7.6%) of the women, after starting progesterone therapy, changed their minds again and either took misoprostol to complete the medical abortion or procured surgical induced abortion. Of those 57, 39 (5.2%) chose to complete abortion medically with misoprostol, seven (0.9%) procured surgical abortions and 11 (1.5%) completed

Figure 1



abortion by unspecified means. These were not included in the analysis as they chose to no longer attempt reversal. See Figure 1.

Women who delivered babies after progesterone therapy or who were lost to follow-up after 20-weeks gestation were considered to have reversed their medical abortions, since any pregnancy loss after 20 weeks would be unlikely to be attributable to the early mifepristone exposure. The data analysis was accomplished using the Statistical Hypothesis Test on a population proportion.

After exclusions, there were 547 patients with analyzable outcomes who underwent progesterone therapy. There were 257 births (47%). Another four were pregnant with viable fetuses but were lost to follow-up after 20 weeks gestation (0.7%). The overall rate of reversal of mifepristone was 48%.

Two subgroups had the highest reversal rates. Those who received progesterone intramuscularly (IM) initially or exclusively had a 64% reversal rate. One subject in this group had an undocumented number of injections. The high-dose oral subgroup received oral progesterone, 400 mg twice a day for three days, followed by 400 mg once a day until the end of the first trimester and had a reversal rate of 68%, similar to the IM group. These survival rates compare favorably with published embryo and fetal survival rate of 25%, if no treatment is attempted,[17] the rate used as a control. See Table 1.

The gestational age at the time of ingestion was directly related to reversal success. See Table 2. This is not surprising since mifepristone embryocidal and feticidal rates fall with advancing gestational age.[33]

There was no correlation between maternal age and rate of reversal. In the subset of records noting time intervals, the time between mifepristone ingestion and the first progesterone dose was not statistically significant in relation to the success rate for reversals attempted within 72 hours of mifepristone injection.

Birth Defects

There were seven reported birth defects in the women who had reversals and follow-up after their deliveries for a rate of 7/257 (2.7%). See Table 3. This is equal to the birth defect rate in the general population of approximately 3%[34] and suggests that there is no increased risk of birth defects in babies born after mifepristone reversal.

Preterm Delivery

There were seven deliveries at <37weeks for a preterm delivery rate of 2.7%. The United States average is 10%.[35]

Multiple Gestations

There were nine sets of twins (4.3% of the pregnancies). There were no higher order multiples.

Discussion

Progesterone Safety

Progesterone is a naturally occurring hormone produced by the corpus luteum and by the placenta, and is essential for maintenance of the maternal fetal interface of pregnancy. It has been used safely in pregnancy for over 50 years.[36] The American Society of Reproductive Medicine states that no long-term risks have been identified when progesterone is used in pregnancy.[37] The FDA has given progesterone a category B rating in pregnancy, in contrast to synthetic progestins.[38]

Table 1: Reversals Compared to Reported Control of 25% Survival if No Treatment Undertaken

All Groups	547	261	286	48%	<0.001	0.44-0.52
High Dose Oral	31	21	10	68%	<0.001	0.51-0.84
Intramuscular, All groups	125	80	45	64%	<0.001	0.56-0.72
IM, 1 Injection	50	24	26	48%	<0.001	0.34-0.62
IM, 2-5 Injec.	36	21	15	58%	<0.001	0.42-0.74
IM, 6-8 Injec.	9	9	0	100%	<0.001	0.67-1
IM, 9-10 Injec.	10	9	1	90%	<0.001	0.77-1.0
IM, 11 or More Injec.	19	17	2	89%	<0.001	0.76-1.0
Oral, All Groups	119	64	55	54%	<0.001	0.45-0.63
Oral Caps Vaginally, All Doses	156	61	95	39%	<0.001	0.31-0.47
Vaginal Suppository	34	11	23	32%	0.161	0.17-0.48

A recent retrospective study of a Danish infertility cohort suggested a possible increased risk of acute lymphocytic leukemia and sympathetic neural tumors in children born to mothers who had taken progesterone during pregnancy and before pregnancy. The increased risk was greatest in women who had taken progesterone for three or more cycles.[39] However, the infertility population examined in the Danish study, exposed to

Table 2: Gestational Age Compared to Reversal Rate

5 weeks	76	19	57	25%	0.5	0.15-0.35
6 weeks	113	52	61	46%	<0.001	0.37-0.55
7 weeks	102	50	52	49%	<0.001	0.39-0.59
8 weeks	88	54	34	61%	<0.001	0.51-0.72
9 weeks	30	23	7	77%	<0.001	0.62-0.92

Table 3: Birth Defects

Port Wine Stain	1
Bilateral Absent Toe	1
Unilateral Two Absent Fingers	1
Choroid Plexus Cyst	1
Cystic Kidney	1
Unilateral Failed Hearing Test	1
Heart Murmur	1

many cycles of progesterone and other medications, differs significantly from our population of fertile women who had a single exposure to progesterone.

Mifepristone Teratogenicity

While previous human studies are not large in number, the available evidence suggests that mifepristone is not teratogenic.[4,40,41] The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin March 2014 states that there is no evidence that mifepristone is associated with teratogenicity.[42] Our data set, the largest of babies exposed to mifepristone in utero, also indicates that the birth defect risk in women who have reversed mifepristone abortions is no higher than the risk in the general population.

Study Limitations

This study is limited in that it is not a randomized placebo-controlled trial. However, a placebo-controlled trial in the population of women who regret their abortion and

want to save the pregnancy would be unethical. Furthermore, although the number of women lost to follow-up was small, it could have affected the results. In addition, some data collection was incomplete.

One potential confounding variable is the use of ultrasound to select for living embryos prior to the first progesterone dose. It is possible that those embryos who were alive at the time of sonogram may have survived without progesterone therapy. However, our study also included some women who started progesterone therapy prior to sonographic documentation that the embryo was alive. Undoubtably, this group included women who already had an embryonic demise prior to initiation of progesterone therapy. Inclusion of these women would falsely lower the success rate of progesterone therapy. The numbers of women who received or did not receive ultrasound exams prior to initiating therapy were not available to our researchers. If ultrasound is readily available, sound practice would dictate that embryonic or fetal viability should be confirmed, or at least suggested, before treatment is started in order to avoid giving women progesterone unnecessarily and to exclude ectopic pregnancy before starting progesterone therapy.

Conclusions

The use of progesterone to reverse the effects of the competitive progesterone receptor blocker, mifepristone, appears to be both safe and effective. Progesterone therapy makes biologic sense, has been previously published as effective in an animal model and is supported by this case series which demonstrates a statistically significant difference in survival between treatment groups and the historic control. Mifepristone is embryocidal and feticidal but not teratogenic; progesterone is not associated with birth defects.

Based on these new data, two reasonable protocols can be suggested for women who seek to reverse the effects of mifepristone:

1. Progesterone micronized 200 mg capsule two by mouth as soon as possible and continued at a dose of 200 mg capsule two by mouth twice a day for three days, followed by 200 mg capsule two by mouth at bedtime until the end of the first trimester; and

2. Progesterone 200 mg intramuscular as soon as possible and continued at a dose of 200 mg intramuscular once a day on days two and three, then every other day for a total of seven injections. Some clinicians may choose to continue intramuscular treatment longer since this recommendation is based on relatively small numbers.

Recommendations for Future Research

We propose that further research employing randomized controlled trials comparing progesterone doses and routes of administration are needed to confirm which mode of delivery, dose and duration of progesterone therapy is most efficacious and carries the least burden for the patient.

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EXHIBIT D

ACOG
The American College of Obstetricians and Gynecologists

Society of Family Planning

ACOG PRACTICE BULLETIN

Clinical Management Guidelines for Obstetrician–Gynecologists

NUMBER 225

(Replaces Practice Bulletin Number 143, March 2014)

Committee on Practice Bulletins—Gynecology and the Society of Family Planning. This Practice Bulletin was developed jointly by the Committee on Practice Bulletins—Gynecology and the Society of Family Planning in collaboration with Mitchell D. Creinin, MD, and Daniel A. Grossman, MD.

Medication Abortion Up to 70 Days of Gestation

Medication abortion, also referred to as medical abortion, is a safe and effective method of providing abortion. Medication abortion involves the use of medicines rather than uterine aspiration to induce an abortion. The U.S. Food and Drug Administration (FDA)-approved medication abortion regimen includes mifepristone and misoprostol. The purpose of this document is to provide updated evidence-based guidance on the provision of medication abortion up to 70 days (or 10 weeks) of gestation. Information about medication abortion after 70 days of gestation is provided in other ACOG publications (1).

Background

Epidemiology

An estimated one in four women in the United States will have an abortion in her lifetime. In 2017, an estimated 60% of abortions in the United States occurred at or before 10 weeks of gestation and medication abortion comprised 39% of all abortions (2). Between 2006 and 2015, there was a shift in the timing of abortion, with abortions taking place at earlier gestational ages; this is likely due, in part, to availability of medication abortion (3). From 2014 to 2017, the number of nonhospital facilities that provided medication abortion increased by 25% (2). A recent survey of American College of Obstetricians and Gynecologists (ACOG) Fellows and Junior Fellows found that 14% had provided medication abortion in the prior year (4).

Medication Abortion

The medication abortion regimen supported by major medical organizations nationally and internationally includes two medications, mifepristone and misoprostol (5, 6). If mifepristone is unavailable, then a misoprostol-only regimen is an acceptable alternative (5). Mifepristone is a selective progesterone receptor modulator that binds to the progesterone receptor with an affinity greater than progesterone itself but does not activate the receptor, thereby acting as an antiprogestin (7). Mifepristone's known actions on a uterus during pregnancy include decidual necrosis, cervical softening, and increased uterine contractility and prostaglandin sensitivity (8, 9). Misoprostol is a prostaglandin E1 analogue that causes cervical softening and uterine contractions. It is approved by the FDA for oral administration to prevent gastric ulcers in individuals who take anti-inflammatory drugs on a long-term basis, and it is included in the FDA-approved labeling of mifepristone for use in abortion (10).

The FDA currently restricts mifepristone access under the risk evaluation and mitigation strategy (REMS) program, which includes a requirement that the drug be "dispensed to patients only in certain health-care settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber" (10). However, the REMS

restrictions for mifepristone do not make the care safer, are not based on medical evidence or need, and create barriers to clinician and patient access to medication abortion (4, 11, 12). The American College of Obstetricians and Gynecologists advocates the removal of REMS restrictions for mifepristone (12).

Clinical Considerations and Recommendations

▶ ***How should patients be counseled about abortion methods?***

Only when patients have considered their options and decided to have an abortion does the discussion about the different methods become clinically relevant. Patients who choose abortion should be counseled about all methods available as well as the risks, advantages, disadvantages, and the different features of these options (5, 6). Most patients who initially are unsure about the method will have some preference after counseling (13). Generally, patients are satisfied with the method they choose (12, 14, 15). Patients who choose medication abortion tend to do so because of a desire to avoid a procedural intervention; a perception that medication abortion is safer, more natural, and private compared with uterine aspiration; or a combination of these reasons (16). Compared with uterine aspiration, medication abortion takes longer to complete and requires more active patient participation as the pregnancy expels outside of a clinical setting. The uterine aspiration procedure for a first-trimester abortion takes place most commonly in one visit, is slightly more effective, and allows for direct assessment of pregnancy tissue by the clinician.

▶ ***What information and counseling should be provided to patients who are considering medication abortion?***

Eligibility and Contraindications

Most patients at 70 days of gestation or less who desire abortion are eligible for a medication abortion. There are medical conditions for which a medication abortion may be preferable to uterine aspiration. Such examples include uterine fibroids that significantly distort the cervical canal or uterine cavity (17, 18), congenital uterine anomalies (19), or introital scarring related to infibulation (20). Patients with asthma are candidates for medication abortion because misoprostol does not cause bronchoconstriction and actually acts as a weak bronchodilator (21). Multiple gestation pregnancy is not a contraindication; patients with twin gestations can be treated with the same regimens as those with singleton gestations (22).

Medication abortion is not recommended for patients with any of the following: confirmed or suspected ectopic pregnancy, intrauterine device (IUD) in place (the IUD can be removed before medication abortion), current long-term systemic corticosteroid therapy, chronic adrenal failure, known coagulopathy or anticoagulant therapy, inherited porphyria, or intolerance or allergy to mifepristone or misoprostol (23). Patients with significant comorbidities may still have a medication abortion but may need more monitoring during the process depending on the stability of the conditions. The safety of medication abortion in patients with anemia is unknown because studies have excluded patients with anemia who have hemoglobin levels of less than 9.5 or 10 g/dL. Although the transfusion rates associated with medication abortion are low (less than 0.1%), they exceed those reported for uterine evacuation procedures in early pregnancy (0.01%) (24, 25). Patients may also not be good candidates for medication abortion if they are unable or unwilling to adhere to care instructions, desire quick completion of the abortion process, are not available for follow-up contact or evaluation, or cannot understand the instructions because of comprehension barriers.

What to Expect

Most patients who have a medication abortion will experience bleeding and cramping, which are necessary for the process to occur. Patient counseling should emphasize that bleeding likely will be much heavier than menses (and potentially with severe cramping).

Adverse effects can occur after mifepristone administration but are more typically experienced after misoprostol administration. Adverse effects commonly associated with misoprostol use include nausea (43–66%), vomiting (23–40%), diarrhea (23–35%), headache (13–40%), dizziness (28–39%), and thermoregulatory effects such as fever, warmth, hot flushes, or chills (32–69%) (26–29). The incidence of each adverse effect varies by regimen used, the dose and route of administration of the prostaglandin analogue, and the gestational age.

Patient counseling before medication abortion should include discussion of when patients should contact their clinician in the case of heavy bleeding (soaking more than two maxi pads per hour for 2 consecutive hours) and when to access urgent intervention (5, 6, 30). In rare cases, patients who undergo medication abortion may need to obtain an additional intervention, such as uterine aspiration. If the prescribing

clinician does not perform the intervention, it is medically appropriate to provide a referral. In patients who receive mifepristone and vaginal misoprostol, the need for intervention within the first 24 hours of treatment is rare, occurring in 0.2% of patients (31). The need for intervention is based on how the patient is feeling and whether the bleeding seems to be slowing. For patients with heavy bleeding, a baseline hemoglobin or hematocrit, if known, may also influence when to seek urgent care. Overall, less than 1% of patients will obtain an emergency intervention for excessive bleeding (13–15, 32), and the need for blood transfusion is rare (0.1% of patients or less) (24, 33). Should a rare medical emergency arise, patients should be advised to seek care at the closest emergency facility.

Teratogenicity and Ongoing Pregnancy

Before undergoing medication abortion, patients should be counseled regarding the teratogenicity of misoprostol in the event of an unsuccessful medication abortion. All patients with a continuing pregnancy after using mifepristone and misoprostol should be provided with all pregnancy options and a thorough discussion of the risks and benefits of each. Most individuals with a continuing pregnancy opt to complete the abortion, but patients should be supported in their choice of how to proceed. No evidence exists to date of a teratogenic effect of mifepristone (34). However, misoprostol can result in congenital anomalies, such as limb defects with or without Möbius' syndrome (ie, facial paralysis), when used during the first trimester (35–39). Because misoprostol is the common agent used with every medication abortion regimen, clinicians should counsel all patients regarding potential teratogenic effects.

In the very rare case that patients change their mind about having an abortion after taking mifepristone and want to continue the pregnancy, they should be monitored expectantly (40). There is no evidence that treatment with progesterone after taking mifepristone increases the likelihood of the pregnancy continuing (41, 42). However, limited available evidence suggests that use of mifepristone alone without subsequent administration of misoprostol may be associated with an increased risk of hemorrhage (43).

▶ *What evaluation and ancillary testing is needed before a medication abortion?*

Before medication abortion is performed, the clinician should confirm pregnancy and estimate gestational age. For patients with regular menstrual cycles, a certain last menstrual period within the prior 56 days, and no signs, symptoms, or risk factors for ectopic pregnancy, a clinical examination or ultrasound examination is not necessary before medication abortion. Rh testing is recommended in patients with unknown Rh status before medication abortion, and Rh D immunoglobulin should be administered if indicated (44). In situations where Rh testing and Rh D immunoglobulin administration are not available or would significantly delay medication abortion, shared decision making is recommended so that patients can make an informed choice about their care. Other laboratory evaluations are not routinely indicated but may be required by local and state laws (2). Preoperative assessment of hemoglobin or hematocrit is indicated only when anemia is suspected.

Most abortion care globally is provided without ultrasound examination. Although most U.S.-based studies have used ultrasonography to confirm gestational age and intrauterine location of the pregnancy, more recent evidence has shown that a patient's certain last menstrual period when within the prior 56 to 63 days is accurate (45–48). In one study, use of certain last menstrual period alone would have resulted in medication abortion being provided to only 26 of 3,041 (0.8%) patients with pregnancies beyond 70 days of gestation (45).

A potential concern when providing early abortion services is the possibility of an undiagnosed ectopic pregnancy. The overall ectopic pregnancy rate in the U.S. general population is low and declining and is approximately 6 per 1,000 pregnancies among insured patients and 14 per 1,000 among patients who receive Medicaid (49, 50). However, in studies of patients who seek abortion, ectopic pregnancy rates generally are lower. A U.S. study of uterine evacuation procedures performed at less than 6 weeks of gestation found the ectopic pregnancy rate to be 5.9 per 1,000 pregnancies (51) at a time when the national rate was three times higher (52). The largest published study of first-trimester medication abortion patients involved 16,369 patients with pregnancies of 49 days of gestation or less and yielded a calculated ectopic pregnancy rate of 1.3 per 1,000 pregnancies (53). Although ectopic pregnancy among individuals who seek early abortion is rare, patients with a medical history of ectopic pregnancy, medical risk factors (prior tubal surgery, pregnancy with progestin-only or IUD contraception use) or symptoms (ie, unilateral pain, vaginal bleeding) suggestive of ectopic pregnancy should have pretreatment clinical evaluation, which may include ultrasonography (5, 6).

Most patients with clinical indications for an ultrasound examination before medication abortion can be initially screened with transabdominal ultrasonography, reserving transvaginal ultrasonography for situations in which further clarification is required (54, 55).

If ultrasonography is medically indicated, transabdominal ultrasonography is sensitive for diagnosing the presence or absence of a gestational sac in patients who are not obese (54). A randomized trial that compared the use of transabdominal ultrasonography with transvaginal ultrasonography for eligibility assessment before medication abortion found that 80% of patients who received initial transabdominal ultrasonography did not require further testing to proceed with medication abortion, thus avoiding use of more invasive and resource-intensive screening with transvaginal ultrasonography (55).

Recommendations on whether Rh D immune globulin should be given to patients before medication abortion in early pregnancy are primarily based on expert opinion because available evidence is limited (6, 56). Rh D alloimmunization that is left undiagnosed and untreated can lead to significant perinatal morbidity and mortality in future pregnancies (57). And, guidelines from ACOG and various other major medical societies include recommendations for Rh D immune globulin prophylaxis for Rh D-negative patients undergoing medication abortion within the first 12 weeks of gestation (44, 58–60). For patients undergoing medication abortion before 10 weeks of gestation, some experts recommend against routine Rh testing and anti-D prophylaxis (6) or advise that forgoing Rh typing and Rh prophylaxis can be considered (61). Research regarding Rh alloimmunization during early pregnancy continues to evolve (62). However, based on currently available indirect evidence and the theoretical risk of Rh D alloimmunization in future pregnancies, ACOG recommends Rh D immune globulin prophylaxis for Rh D-negative patients undergoing medication abortion. In situations where Rh testing and anti-D prophylaxis are not available or would significantly delay medication abortion, shared decision making is recommended so that patients can weigh the benefits and risks of their options and make an informed decision about their care.

▶ *What regimens are used for medication abortion, and how do they compare in effectiveness for treatment?*

Combined mifepristone–misoprostol regimens are recommended as the preferred therapy for medication abortion because they are significantly more effective than misoprostol-only regimens. If a combined mifepristone–misoprostol regimen is not available, a misoprostol-only regimen is the recommended alternative (5, 63, 64). Mifepristone is approved by the U.S. FDA to be used with misoprostol for medication abortion through 70 days of gestation (23), but evidence also exists to support use with more advanced gestations (1, 5). The recommended medication abortion regimens are listed in Table 1. With all regimens, the mifepristone dose is the same: 200 mg taken orally. The misoprostol portion of the regimen is more variable in terms of dose, route, and timing. Oral use of misoprostol is not recommended because it may result in lower overall efficacy (65). In general, patients prefer a shorter interval between the two medications (66). These regimens have been extensively studied and are similarly safe and effective (5). Offering options provides patients with flexibility in the timing of abortion and the ability to avoid possible adverse effects related to the misoprostol route. Gastrointestinal adverse effects are less common when misoprostol is administered vaginally as compared with regimens that use oral, buccal, or sublingual misoprostol (65, 67). Buccal and sublingual administration cause similar adverse effects, with the sublingual route associated with a higher rate of chills (68).

Complete abortion rates with all regimens are highest at earlier gestational ages (Table 2). *Medication abortion failure* (defined as the need for uterine aspiration because of ongoing pregnancy or retained tissue) increases with advancing gestational age through 70 days of gestation (Table 2), although failure rates remain low even at this point. Clinicians should counsel patients that medication abortion failure rates, especially continuing pregnancy rates, increase as gestational age approaches 10 weeks.

▶ *Who is qualified to provide medication abortion, and in what settings can medication abortion be provided?*

Any clinician with the skills to screen patients for eligibility for medication abortion and to provide appropriate follow-up can provide medication abortion. Clinicians who wish to provide medication abortion services should be trained to perform uterine evacuation procedures or should be able to refer to a clinician who has this training (5, 69).

In addition to physicians, advanced practice clinicians, such as nurse–midwives, physician assistants, and nurse practitioners, possess the clinical and counseling skills necessary to provide first-trimester medication abortion (70). Randomized trials in Mexico, Nepal, and Sweden have consistently found that patients randomized to receive medication abortion under the care of a nurse or nurse–midwife had a statistically equivalent risk of complete abortion compared with those under the care of a physician, without increased risk of adverse events (71–73). In some U.S. states, advance practice clinicians can provide medication abortion; however, many states require that a physician perform an abortion and prohibit provision of medication abortion by nonphysician clinicians (2).

Table 1. Medication Abortion Regimens Up to 70 Days of Gestation

Regimen	Mifepristone Dose	Misoprostol Dose	Interval Between Drugs
		Preferred	
Combination, FDA-approved*	200 mg (orally)	800 micrograms (buccally)	24–48 h
Combination, WHO recommended†	200 mg (orally)	800 micrograms (vaginally, sublingually, or buccally)	24–48 h
		Alternative	
Misoprostol only	N/A	800 micrograms (vaginally, sublingually, or buccally)	Repeat every 3 h for up to 3 doses‡

Abbreviations: h, hours; FDA, U.S. Food and Drug Administration; N/A, not applicable; WHO, World Health Organization.

*U.S. Food and Drug Administration. Mifeprex (mifepristone) information. Postmarket drug safety information for patients and providers. Silver Spring, MD: FDA; 2018. Available at: https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111323.htm. Retrieved March 3, 2020.

†World Health Organization. Medical management of abortion. Geneva: WHO; 2018. Available at: https://apps.who.int/iris/bitstream/handle/10665/278968/9789241550406-eng.pdf?ua=1. Retrieved March 3, 2020.

‡Although studies typically use no more than three doses for the initial treatment regimen, the World Health Organization guidelines do not specify a maximum number of misoprostol doses (Raymond EG, Harrison MS, Weaver MA. Efficacy of misoprostol alone for first-trimester medical abortion: a systematic review. Obstet Gynecol 2019;133:137-47 *and* World Health Organization. Medical management of abortion. Geneva: WHO; 2018. Available at: https://apps.who.int/iris/bitstream/handle/10665/278968/9789241550406-eng.pdf?ua=1. Retrieved March 3, 2020).

According to the requirements of the FDA REMS program, clinicians who want to prescribe mifepristone must complete a "prescriber agreement form" before ordering and dispensing mifepristone, and the clinician and patient need to sign a "patient agreement form" before the drug is dispensed (10).

The actual location of where a patient takes the medication abortion drugs has evolved over time. Although the FDA REMS program for mifepristone continues to require dispensing in the clinician's office, the U.S. labeling for mifepristone no longer indicates that the medication should be used only in the clinician's office (10). Patients can safely and effectively use mifepristone at home for medication abortion (74–77). A clinician can prescribe misoprostol and pain medications or can maintain an office supply and directly dispense to the patient. Patients can safely and effectively self-administer misoprostol at home for medication abortion (5, 78–80).

Medication abortion can be provided safely and effectively by telemedicine with a high level of patient satisfaction, and telemedicine improves access to early abortion care, particularly in areas that lack a health care practitioner (81, 82). Telemedicine involves the use of video and information technology to provide a medical service at a distance. Medication abortion through telemedicine has been evaluated in observational studies and found to be equally effective as an in-person visit (33, 83–85). In an analysis of nearly 20,000 medication abortions, adverse events were rare (0.3% overall) and did not differ between those who choose telemedicine or in-person services (33, 84). Patients who choose telemedicine medication abortion are significantly more likely to say they would recommend the service to a friend compared with those who have an in-person visit (90% versus 83%) (83). Telemedicine also may help reduce the rate of delays to care because of barriers in access to abortion care in remote areas (82). After medication abortion through telemedicine was introduced in Iowa, a significant reduction in second-trimester abortion was reported, and patients in remote parts of the state were more likely to obtain a medication abortion (82). Despite this evidence, some states have passed legislation that bans the use of telemedicine to provide medication abortion (86).

▶ *Should prophylactic antibiotics be used in medication abortion?*

The routine use of prophylactic antibiotics is not recommended for medication abortion (6). Following concern about serious, rare, and deadly infection with clostridial bacteria in patients undergoing medication abortion, it has since become evident that no specific connection exists between clostridial organisms and medication abortion (87, 88). Uterine infection with medication abortion is uncommon, and published data do not support the routine use of prophylactic antibiotics in medication abortion. In a systematic review of 65 studies

Table 2. Outcome by Gestational Age After Mifepristone 200 mg and Misoprostol for Outpatient Medication Abortion

	Misoprostol Dose	Interval Between Mifepristone and Misoprostol (h)	Gestational Age			
			≤49 days	50–56 days	57–63 days	64–70 days
Complete abortion	800 micrograms buccally[*]	24–48	98.1%	96.8%	94.7%	92.7%
	800 micrograms vaginally[†‡§‖¶‡‡]	24–72	98.3–99.7%	95.3–98.6%	95.1–98.3%	94.9%
	800 micrograms vaginally[§]	6–8	97.1%	94.2%	95.2%	N/A
	800 micrograms vaginally[‖¶]	0–0.25	95.5–95.7%	93.7–94.3%	91.6–95.3%	N/A
	400 micrograms sublingually[#**]	24–48	95.4%	N/A	94.8%	91.9%
Ongoing pregnancy	800 micrograms buccally[*]	24–48	0.3%	0.8%	2.0%	3.1%
	800 micrograms vaginally[†‡§‖¶‡‡]	24–72	0–0.4%	0–1.2%	0–2.2%	3.4%
	800 micrograms vaginally[§]	6–8	0.4%	0	0.8%	N/A
	800 micrograms vaginally[‖¶]	0–0.25	1.4–2.3%	1.9–2.8%	1.6–5.0%	N/A
	400 micrograms sublingually[#**††]	24–48	N/A	N/A	1.8–3.5%	2.2%

Abbreviations: h, hours; N/A, not available.

*U.S. Food and Drug Administration. Mifeprex (mifepristone) information. Postmarket drug safety information for patients and providers. Silver Spring, MD: FDA; 2018. Available at: https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111323.htm. Retrieved March 3, 2020.

†Schaff EA, Eisinger SH, Stadalius LS, Franks P, Gore BZ, Poppema S. Low-dose mifepristone 200 mg and vaginal misoprostol for abortion. Contraception 1999;59:1–6.

‡Schaff EA, Fielding SL, Westhoff C. Randomized trial of oral versus vaginal misoprostol at one day after mifepristone for early medical abortion. Contraception 2001;64:81–5.

§Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. A randomized comparison of misoprostol 6 to 8 hours versus 24 hours after mifepristone for abortion. MOD Study Trial Group. Obstet Gynecol 2004;103:851–9.

‖Creinin MD, Schreiber CA, Bednarek P, Lintu H, Wagner MS, Meyn LA. Mifepristone and misoprostol administered simultaneously versus 24 hours apart for abortion: a randomized controlled trial. Medical Abortion at the Same Time (MAST) Study Trial Group. Obstet Gynecol 2007;109:885–94.

¶Lohr PA, Starling JE, Scott JG, Aiken AR. Simultaneous compared with interval medical abortion regimens where home use is restricted [published erratum appears in Obstet Gynecol 2018;132:219]. Obstet Gynecol 2018;131:635–41.

#Raghavan S, Tsereteli T, Kamilov A, Kurbanbekova D, Yusupov D, Kasimova F, et al. Acceptability and feasibility of the use of 400 μg of sublingual misoprostol after mifepristone for medical abortion up to 63 days since the last menstrual period: evidence from Uzbekistan. Eur J Contracept Reprod Health Care 2013;18:104–11.

**Bracken H, Dabash R, Tsertsvadze G, Posohova S, Shah M, Hajri S, et al. A two-pill sublingual misoprostol outpatient regimen following mifepristone for medical abortion through 70 days' LMP: a prospective comparative open-label trial. Contraception 2014;89:181–6.

††von Hertzen H, Huong NT, Piaggio G, Bayalag M, Cabezas E, Fang AH, et al. Misoprostol dose and route after mifepristone for early medical abortion: a randomised controlled noninferiority trial. WHO Research Group on Postovulatory Methods of Fertility Regulation. BJOG 2010;117:1186–96.

‡‡Hsia JK, Lohr PA, Taylor J, Creinin MD. Medical abortion with mifepristone and vaginal misoprostol between 64 and 70 days' gestation. Contraception 2019;100:178–81.

of heterogeneous design (prospective, retrospective, and randomized), the overall proportion of diagnosed or treated infection after medication abortion was 0.9% in more than 46,000 patients (89). In these studies, as in most studies of abortion by uterine evacuation, the diagnostic criteria for infection were variable, leading to possible overestimation of infection.

Although serious infections occur rarely in patients after medication abortion, clinicians need to be aware of the signs and symptoms. Tachycardia, severe abdominal pain, or general malaise with or without fever that occur more than 24 hours after misoprostol administration should increase suspicion of a serious infection (90). Clostridial toxic shock often resembles a flu-like illness, so clinicians should have a high level of suspicion for infection when symptoms consistent with flu are present (90). Patients with such infections typically have hemoconcentration and significant leukocytosis without fever and can rapidly progress to refractory hypotension and death (91).

▶ ***What is the recommended pain management approach for patients undergoing medication abortion?***

Nonsteroidal anti-inflammatory drugs are recommended for pain management in patients who undergo a medication abortion. Pain management during medication abortion is an important consideration because many patients report pain that requires analgesia. Studies of pain control and medication abortion have found that the duration of pain for most patients is no longer than 24 hours after misoprostol administration (92, 93). The most severe pain occurs approximately 2.5–4 hours after misoprostol use and lasts about 1 hour (94). One randomized trial found that ibuprofen taken when needed was more effective than acetaminophen to reduce pain associated with medication abortion (95). Another randomized trial found ibuprofen given prophylactically at the time of misoprostol administration did not significantly reduce pain associated with medication abortion compared with ibuprofen taken when needed (93). Nonsteroidal anti-inflammatory drugs do not appear to counteract misoprostol or affect the success of the medication abortion (96). Opioids have not been found to decrease the amount or duration of maximum pain associated with medication abortion up to 70 days of gestation (94). Other medications, like pregabalin, have been studied for pain control but have not been effective (97).

Patients should be sent home with appropriate instructions for analgesia with over-the-counter medications. If opioids are requested or desired, the Centers for Disease Control and Prevention (CDC) advises that "clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids" (98).

▶ ***What kind of assessment is recommended after medication abortion?***

Routine in-person follow-up is not necessary after uncomplicated medication abortion. Clinicians should offer patients the choice of self-assessment or clinical follow-up evaluation to assess medication abortion success. If medically indicated or preferred by the patient, follow-up evaluation can be performed by medical history, clinical examination, serum human chorionic gonadotropin (hCG) testing, or ultrasonography (5, 6, 99).

The type of follow-up visit after medication abortion has evolved over time. The mifepristone FDA label includes recommendations for follow up (23). However, some patients choose not to return for follow-up; this likely is due to the high success rates and because patients are able to self-assess abortion completion (100–102).

Remote Assessment and Self-Assessment

Follow-up can be performed by telephone at 1 week, with subsequent at-home urine pregnancy testing at 4 weeks after treatment, which avoids the need for the patient to go to a facility (103–106). Most studies have used a short series of questions that ask patients whether they have experienced bleeding and cramping (including how much and for how long) and whether they still feel pregnant or if they think the pregnancy has passed (104, 107). When the clinician and the patient think that expulsion has occurred based on symptomatology, they are correct 96–99% of the time (104, 108). Although urine pregnancy testing alone with standard high-sensitivity or low-sensitivity tests has not been shown to be a viable alternative to other forms of follow-up, newer semiquantitative or multilevel at-home urine hCG tests have shown promise in accurately identifying ongoing pregnancies after medication abortion (109–112).

Clinical Follow-Up

When a patient obtains in-person follow-up after medication abortion, transvaginal ultrasonography is commonly used, although it is not required (5). If an ultrasound examination is performed at follow-up after medication abortion, the sole purpose is to determine whether the gestational sac is present or absent. The measurement of endometrial thickness or other findings do not predict the need for subsequent uterine aspiration (113). In research trials, when a transvaginal ultrasound examination shows no evidence of a gestational sac

1 week after mifepristone use, only 1.6% of patients needed subsequent uterine evacuation (113).

Serum hCG testing before treatment and 1 week after treatment is another option for follow-up examination after medication abortion; however, data about use of this approach are lacking for gestations beyond 63 days. This strategy may be more effective than ultrasonography to confirm abortion completion in patients who were below the threshold for visualization of a gestational sac at the time of their medication abortion (114). Patients do not need to return to the same facility; they can obtain serum hCG testing at a convenient location (114, 115). The patient should then be informed of the result. A serum hCG level decrease of at least 80% over 6–7 days after initiating treatment with mifepristone and misoprostol indicates a successful abortion (114). In a randomized trial of in-clinic transvaginal ultrasound examination or serum hCG testing follow-up, 24.5% of patients were lost to follow-up, there were no significant differences reported in unplanned visits and interventions by 2 weeks (6.6% versus 8.2%, respectively) or in uterine evacuation rates by 4 weeks (4.4% and 1.4%, respectively) (116).

▶ *How is incomplete medication abortion or ongoing pregnancy managed?*

Guidelines for intervention vary for patients who have delayed expulsion, an incomplete medication abortion (ie, persistent gestational sac on ultrasonography without evidence of embryonic cardiac activity or retained tissue), or an ongoing pregnancy (ie, continuing development with embryonic cardiac activity).

Delayed Expulsion

After induced or spontaneous expulsion, the uterus will normally contain sonographically hyperechoic tissue or "thick" endometrial stripe that consists of blood, blood clots, and decidua. Rarely does this ultrasound finding in patients who have undergone medication abortion indicate a need for intervention. In the absence of excessive bleeding or pain by patient report, clinicians can monitor such patients based on symptoms.

Incomplete Medication Abortion

An incomplete medication abortion can be treated with a repeat dose of misoprostol, uterine aspiration, or expectant management, depending on the clinical circumstances and patient preference (23, 30, 117, 118). Studies indicate that even with a retained sac at 2 weeks after medication abortion, intervention is unnecessary, and that expulsion will typically occur in the ensuing weeks (30). However, some patients with incomplete expulsion will have bothersome symptoms, such as prolonged and irregular bleeding episodes. Patients with incomplete medication abortion 1 week after treatment can safely receive another dose of misoprostol (28, 118) or repeat misoprostol doses can be used for a persistent gestational sac (117). Patients who prefer not to wait or do not desire medical management can choose to have a uterine evacuation at any time.

Ongoing Pregnancy

Ongoing pregnancy after medication abortion can be treated with a repeat dose of misoprostol or uterine aspiration, depending on the clinical circumstances and patient preference. In an analysis of data from two randomized trials with 14 cases of ongoing pregnancy, treatment with a repeat dose of misoprostol, 800 micrograms administered vaginally, resulted in expulsion of the products of pregnancy in five cases (36%); in an additional four cases (29%), gestational cardiac activity was no longer present at the next follow-up visit (118). If gestational cardiac activity persists at follow-up after a second dose of misoprostol, uterine aspiration should be performed.

▶ *What is the recommended timing of contraception initiation after medication abortion?*

Patients undergoing medication abortion who desire contraception should be counseled that

- almost all contraceptive methods, except IUDs and permanent contraception, can be safely initiated immediately on day 1 (mifepristone intake) of medication abortion.
- all contraceptive methods can be safely initiated after successful medication abortion.

Patients who select depot medroxyprogesterone acetate (DMPA) for contraception should be counseled that administration of DMPA on day 1 of the medication abortion regimen may increase the risk of ongoing pregnancy (119).

Providing desired contraception as soon as possible to patients undergoing medication abortion enables the greatest flexibility in care and decreases barriers to initiating contraception. The CDC and World Health Organization (WHO) support the initiation of almost all methods of contraception on day 1 of the medication abortion or on the same day as mifepristone administration (5, 6, 120). Permanent contraception procedures may be performed once abortion is confirmed complete.

Concern has been raised that the immediate use of hormonal contraception that contains progestins could theoretically interfere with medication abortion efficacy. Etonogestrel implant use does not affect medication abortion outcomes (121, 122). However, DMPA injection at the time of mifepristone administration may slightly increase the risk of an ongoing pregnancy

(119). In a randomized trial that evaluated the effects of DMPA injection timing on medication abortion outcomes, ongoing pregnancy was more common among those randomized to receive DMPA injection on the day of mifepristone administration compared with those who received DMPA at a follow-up visit (3.6% versus 0.9%; 90% CI, 2.7 [0.4–5.6]), although the proportion undergoing aspiration for any reason did not significantly vary (6.4% versus 5.3%; 90% CI, 1.1 [–2.8 to 4.9]) (119). Patients should be counseled about this small risk of ongoing pregnancy, which needs to be weighed against the risk of potentially not receiving their desired method of contraception.

Patients do not experience a higher rate of IUD expulsion with placement in the first week after medication abortion as compared with 3 to 6 weeks later (123, 124). However, IUD placement within 6 weeks after medication abortion is associated with a higher expulsion rate compared with IUD placement remote from pregnancy; the time frame after 6 weeks at which this rate decreases is unknown. Placement of a copper or levonorgestrel IUD close to the time of abortion results in improved uptake of a desired IUD compared with placement at an additional follow-up visit several weeks after the abortion (123–125), although overall use rates at 6 months may not differ (126). The IUD expulsion risk should be weighed against the potential for more patients to receive their desired IUD if it is placed sooner rather than later.

▶ *How should patients be counseled about the effect of medication abortion on future fertility and pregnancy outcomes?*

Patients can be counseled that medication abortion does not have an adverse effect on future fertility or future pregnancy outcomes (5, 6). Studies consistently demonstrate that medication abortion has no negative effect on future fertility or pregnancy outcomes. A study from China found that patients who had a prior mifepristone abortion had lower odds of preterm birth compared with those who had never been pregnant (adjusted OR, 0.77; 95% CI, 0.61–0.98), and the frequencies of low-birth-weight infants and mean lengths of pregnancy were similar in both groups (127). No significant differences were reported in risk of preterm delivery, frequency of low-birth-weight infants, or mean infant birth weight in the comparisons of patients who had previous mifepristone abortion and patients who had uterine evacuation. In a registry-based study from Scotland, no association was found between prior abortion and subsequent preterm birth during the period 2000−2008, when 68% of abortions were medication-induced (128).

Summary of Recommendations

The following recommendations are based on good and consistent scientific evidence (Level A):

- Combined mifepristone–misoprostol regimens are recommended as the preferred therapy for medication abortion because they are significantly more effective than misoprostol-only regimens. If a combined mifepristone–misoprostol regimen is not available, a misoprostol-only regimen is the recommended alternative.
- Clinicians should counsel patients that medication abortion failure rates, especially continuing pregnancy rates, increase as gestational age approaches 10 weeks.
- Any clinician with the skills to screen patients for eligibility for medication abortion and to provide appropriate follow-up can provide medication abortion.
- Patients can safely and effectively use mifepristone at home for medication abortion.
- Patients can safely and effectively self-administer misoprostol at home for medication abortion.
- Nonsteroidal anti-inflammatory drugs are recommended for pain management in patients who undergo a medication abortion.
- Routine in-person follow-up is not necessary after uncomplicated medication abortion. Clinicians should offer patients the choice of self-assessment or clinical follow-up evaluation to assess medication abortion success. If medically indicated or preferred by the patient, follow-up evaluation can be performed by medical history, clinical examination, serum human chorionic gonadotropin (hCG) testing, or ultrasonography.
- If an ultrasound examination is performed at follow-up after medication abortion, the sole purpose is to determine whether the gestational sac is present or absent. The measurement of endometrial thickness or other findings do not predict the need for subsequent uterine aspiration.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- Medication abortion is not recommended for patients with any of the following: confirmed or suspected ectopic pregnancy, intrauterine device (IUD) in place (the IUD can be removed before medication abortion), current long-term systemic corticosteroid therapy, chronic adrenal failure,

known coagulopathy or anticoagulant therapy, inherited porphyria, or intolerance or allergy to mifepristone or misoprostol.

- Before undergoing medication abortion, patients should be counseled regarding the teratogenicity of misoprostol in the event of an unsuccessful medication abortion.
- Before medication abortion is performed, the clinician should confirm pregnancy and estimate gestational age. For patients with regular menstrual cycles, a certain last menstrual period within the prior 56 days, and no signs, symptoms, or risk factors for ectopic pregnancy, a clinical examination or ultrasound examination is not necessary before medication abortion.
- Most patients with clinical indications for an ultrasound examination before medication abortion can be initially screened with transabdominal ultrasonography, reserving transvaginal ultrasonography for situations in which further clarification is required.
- Medication abortion can be provided safely and effectively by telemedicine with a high level of patient satisfaction.
- The routine use of prophylactic antibiotics is not recommended for medication abortion.
- An incomplete medication abortion can be treated with a repeat dose of misoprostol, uterine aspiration, or expectant management, depending on the clinical circumstances and patient preference.
- Ongoing pregnancy after medication abortion can be treated with a repeat dose of misoprostol or uterine aspiration, depending on the clinical circumstances and patient preference.
- Patients undergoing medication abortion who desire contraception should be counseled that
  - almost all contraceptive methods, except IUDs and permanent contraception, can be safely initiated immediately on day 1 (mifepristone intake) of medication abortion.
  - all contraceptive methods can be safely initiated after successful medication abortion.
- Patients who select depot medroxyprogesterone acetate (DMPA) for contraception should be counseled that administration of DMPA on day 1 of the medication abortion regimen may increase the risk of ongoing pregnancy.
- Patients can be counseled that medication abortion does not have an adverse effect on future fertility or future pregnancy outcomes.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- Patients who choose abortion should be counseled about all methods available as well as the risks, advantages, disadvantages, and the different features of these options.
- Most patients at 70 days of gestation or less who desire abortion are eligible for a medication abortion.
- Patient counseling before medication abortion should include discussion of when patients should contact their clinician in the case of heavy bleeding (soaking more than two maxi pads per hour for 2 consecutive hours) and when to access urgent intervention.
- All patients with a continuing pregnancy after using mifepristone and misoprostol should be provided with all pregnancy options and a thorough discussion of the risks and benefits of each.
- In the very rare case that patients change their mind about having an abortion after taking mifepristone and want to continue the pregnancy, they should be monitored expectantly.
- Rh testing is recommended in patients with unknown Rh status before medication abortion, and Rh D immunoglobulin should be administered if indicated. In situations where Rh testing and Rh D immunoglobulin administration are not available or would significantly delay medication abortion, shared decision making is recommended so that patients can make an informed choice about their care.
- Clinicians who wish to provide medication abortion services should be trained to perform uterine evacuation procedures or should be able to refer to a clinician who has this training.

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 2000 and February 2020. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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This information is designed as an educational resource to aid clinicians in providing obstetric and gynecologic care, and use of this information is voluntary. This information should not be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. It is not intended to substitute for the independent professional judgment of the treating clinician. Variations in practice may be warranted when, in the reasonable judgment of the treating clinician, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology. The American College of Obstetricians and Gynecologists reviews its publications regularly; however, its publications may not reflect the most recent evidence. Any updates to this document can be found on acog.org or by calling the ACOG Resource Center.

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EXHIBIT E

August 2017

ACOG
THE AMERICAN CONGRESS OF OBSTETRICIANS AND GYNECOLOGISTS

Facts Are Important:
Medication Abortion "Reversal" Is Not Supported by Science

Facts are important, especially when discussing the health of women and the American public. Claims regarding abortion "reversal" treatment are not based on science and do not meet clinical standards. The American College of Obstetricians and Gynecologists (ACOG) ranks its recommendations on the strength of the evidence,[i] and does not support prescribing progesterone to stop a medical abortion.

Yet, politicians are pushing legislation to require physicians to recite a script that a medication abortion can be "reversed" with doses of progesterone, and to steer women to this care. Unfounded legislative mandates represent dangerous political interference and compromise patient care and safety.

What is Medication Abortion?

- Medication abortion is the use of medications, rather than surgery, to end a pregnancy. This safe and effective evidence-based regimen includes a combination of two drugs—mifepristone, taken first, and misoprostol, taken at a later point.
- Mifepristone stops the pregnancy growth by blocking the hormone progesterone; misoprostol makes the uterus contract to complete the abortion.
- Medication abortion is more effective when both drugs are used, because mifepristone alone will not always cause abortion. In fact, as many as half of women who take only mifepristone continue their pregnancies. [ii]
- Mifepristone is not known to cause birth defects.

So-called abortion "reversal" procedures are unproven and unethical.

- A 2012 case series reported on six women who took mifepristone and were then administered varying progesterone doses. Four continued their pregnancies.[iii] This is not scientific evidence that progesterone resulted in the continuation of those pregnancies.
- This study was not supervised by an institutional review board (IRB) or an ethical review committee, required to protect human research subjects, raising serious questions regarding the ethics and scientific validity of the results.
- Case series with no control groups are among the weakest forms of medical evidence.[iv]

Legislative mandates based on unproven, unethical research are dangerous to women's health.

Politicians should never mandate treatments or require that physicians tell patients inaccurate information.

Additional ACOG Resources:

- ACOG Practice Bulletin 143 *Medical Management of First-Trimester Abortion* (March 2014)

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[i] Hal C. Lawrence, M.D., "The American College of Obstetricians and Gynecologists Supports Access to Women's Health Care," *Obstetrics & Gynecology* vol. 125 1282, 1283 (Jun. 2015) available at http://journals.lww.com/greenjournal/Fulltext/2015/06000/The_American_College_of_Obstetricians_and.2.aspx.

[ii] Grossman D et al. "Continuing Pregnancy After Mifepristone and 'Reversal' of First-Trimester Medical Abortion: A Systematic Review," *Contraception* 92 206–211 (Jun. 2015).

[iii] Delgado G and Davenport M, "Progesterone Use to Reverse the Effects of Mifepristone," *The Annals of Pharmacotherapy* vol. 46 (Dec. 2012).

[iv] ACOG, *Reading the Medical Literature*, available at http://www.acog.org/Resources-And-Publications/Department-Publications/Reading-the-Medical-Literature.

EXHIBIT F

Contraception

Contraception 92 (2015) 206–211

Review article

Continuing pregnancy after mifepristone and "reversal" of first-trimester medical abortion: a systematic review☆

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Abstract

Objective: We conducted a systematic review of the literature on the effectiveness of medical abortion "reversal" treatment. Since the usual care for women seeking to continue pregnancies after ingesting mifepristone is expectant management with fetal surveillance, we also performed a systematic review of continuing pregnancy after mifepristone alone.
Study design: We searched PubMed, CINAHL (*Cumulative Index to Nursing and Allied Health Literature*), Scopus and the Cochrane Library for articles published through March 2015 reporting the proportion of pregnancies continuing after treatment with either mifepristone alone or after an additional treatment following mifepristone aimed at reversing its effect.
Results: From 1115 articles retrieved, 1 study met inclusion criteria for abortion reversal, and 13 studies met criteria for continuing pregnancy after mifepristone alone. The one report of abortion reversal was a case series of 7 patients receiving varying doses of progesterone in oil intramuscularly or micronized progesterone orally or vaginally; 1 patient was lost to follow-up. The study was of poor quality and lacked clear information on patient selection. Four of six women continued the pregnancy to term [67%, 95% confidence interval (CI) 30–90%]. Assuming the lost patient aborted resulted in a continuing pregnancy proportion of 57% (95% CI 25–84%). The proportion of pregnancies continuing 1–2 weeks after mifepristone alone varied from 8% (95% CI 3–22%) to 46% (95% CI 37–56%). Continuing pregnancy was more common with lower mifepristone doses and advanced gestational age.
Conclusions: In the rare case that a woman changes her mind after starting medical abortion, evidence is insufficient to determine whether treatment with progesterone after mifepristone results in a higher proportion of continuing pregnancies compared to expectant management.
Implications: Legislation requiring physicians to inform patients about abortion reversal transforms an unproven therapy into law and represents legislative interference in the patient–physician relationship.

Keywords: Medical abortion; Mifepristone; Reversal; Progesterone; Continuing pregnancy

1. Introduction

First-trimester medical abortion involves the use of mifepristone followed by misoprostol, generally up to a gestational age of 63 days from last menstrual period [1,2]. Many women prefer medical abortion to surgical abortion

☆ Conflicts of interest: none.

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0010-7824/

because they perceive it as less invasive and more private [3]. The proportion of all nonhospital abortions in the United States that were early medical abortions increased from 17% in 2008 to 23% in 2011 [4].

In early 2015, legislatures in Arizona and Arkansas passed laws requiring physicians providing abortion to inform women that if they choose to have a medical abortion and then decide not to complete the abortion, the effect of mifepristone may be reversed with specific treatment [5]. Treatment to reverse the effects of mifepristone is not considered an established practice by the American College of Obstetricians and Gynecologists (ACOG) [6] and was not described in a recent practice bulletin on first-trimester medical abortion issued by ACOG and the Society of Family Planning (SFP) [1].

The purpose of this study was to perform a systematic review of the literature on reversal of medical abortion that documented the proportion of pregnancies continuing after treatment. Since the usual care for women seeking to continue pregnancies after ingesting mifepristone is expectant management with fetal surveillance, we also performed a systematic review of continuing pregnancy after treatment with mifepristone alone.

2. Materials and methods

2.1. Systematic review of medical abortion reversal

In this review, we searched for reports of pharmacological methods (e.g., intramuscular injection of progesterone) to reverse the effects of mifepristone prior to administration of misoprostol (or any other prostaglandin) for first-trimester medical abortion. We anticipated few, if any, randomized controlled trials and therefore broadened our search to include cohort studies and case studies or case series; we excluded review articles, editorials and commentaries. The primary outcome was the proportion of women who carried their pregnancies to term after receiving treatment to reverse the effect of mifepristone.

We searched for studies published through March 31, 2015, using databases for PubMed, the CINAHL (*Cumulative Index to Nursing and Allied Health Literature*), Scopus and the Cochrane Library. We combined the following search terms as Medical Subject Headings (MeSH) and text words: induced abortion, steroidal abortifacient agents; mifepristone; Mifeprex; Mifegyne; RU-486; reverse; antidote; progesterone; progestin; first-trimester pregnancy (see Box).

After initial title and abstract screening, two reviewers (DG and KW) independently evaluated full-text articles to determine whether they met the inclusion criteria. For relevant studies, we recorded the number of women enrolled in the study (or included in the case series) and the number of continuing pregnancies. We then calculated the percentage of continuing pregnancies and 95% Wilson Score confidence intervals (CIs) for women receiving reversal therapy.

Box
List of PubMed search terms used in a systematic review of studies on the efficacy of medical abortion reversal

Search	
(1)	"Abortifacient Agents, Steroidal"[mesh] or "Mifepristone" [mesh] or mifepristone or mifegyne or mifeprex or "r 38486" or r38486 or r-38486 or "ru 38486" or "ru 486" or ru486 or ru-486 or ru38486 or "zk 98296" or zk98296 or zk-98296
(2)	"Abortion, Induced"[mesh] or abort* or terminat*
(3)	("Pregnancy"[mesh] or pregnan* and ("first trimester") or (week*)) or "Pregnancy Trimester, First"[mesh] or "early pregnancy"
(4)	revers* or antidote or "Progesterone"[mesh] or progesterone or "progestins"[mesh] or progestin*
	#1 AND #2 AND #3 AND #4 AND (("0001/01/01"[PDAT]: "2015/03/31"[PDAT]) AND "humans"[MeSH Terms])

2.2. Systematic review of continuing pregnancies following the use of mifepristone alone for first-trimester medical abortion

We reviewed cohort studies and randomized controlled trials that used mifepristone alone during the first trimester of pregnancy to induce abortion, which we identified through a search of the same four databases and using the same search strategy, excluding the reversal terms. We also searched the reference lists of relevant publications for additional studies. We excluded studies that only reported medical abortion failure after mifepristone alone and did not specify the number of continuing pregnancies. We calculated the proportion of pregnancies continuing at the time of the follow-up visit after treatment with mifepristone alone and 95% Wilson Score CIs. Because the mifepristone regimens were not uniform, metaanalysis could not be performed.

3. Results

3.1. Systematic review of medical abortion reversal

Of the 319 unduplicated titles identified in our search, one article met our inclusion criteria (Fig. 1). This article was a case series by Delgado and Davenport [7] of seven women who received progesterone treatment after taking mifepristone for medical abortion at 7–11 weeks gestation. The mifepristone dosage was not noted. One patient was lost to follow-up. Of the six patients with follow-up data, four continued the pregnancy and delivered at term with no apparent congenital malformations; two patients aborted the pregnancy within 3 days of taking mifepristone. The progesterone regimen varied from progesterone in oil 200 mg intramuscularly daily to twice per week, sometimes followed by oral micronized progesterone, to micronized

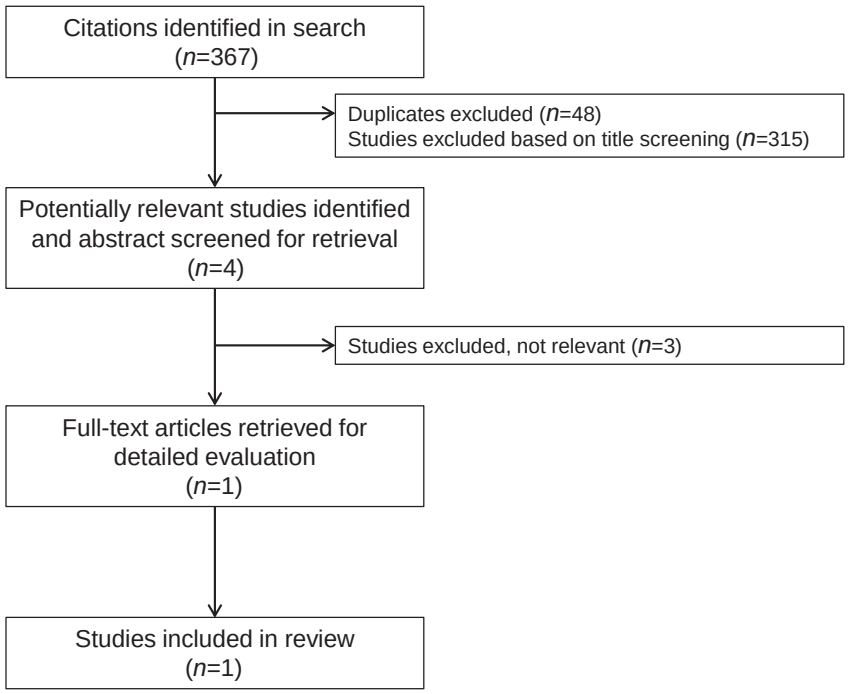

Fig. 1. Summary of study selection process for medical abortion reversal.

progesterone administered vaginally. Therapy was continued for up to 5 months. The publication provides limited details, but it appears that, in at least five cases, a living embryo was documented prior to initiating progesterone treatment. The authors did not report how many women presented seeking medical abortion reversal after taking mifepristone and were found to have already aborted and therefore excluded from treatment. The dates during which cases were collected are not specified, and it is unclear if all women treated were included in the case series. Based on the four continuing pregnancies and excluding the patient lost to follow-up, the proportion of pregnancies continuing after this therapy was 67% (95% CI 30–90%). If we assume that the patient lost to follow-up had an abortion, the continuing pregnancy proportion was 57% (95% CI 25–84%).

3.2. Systematic review of continuing pregnancies following the use of mifepristone alone for first-trimester medical abortion

Our search retrieved 1115 unduplicated articles, and 13 studies in 11 publications met our inclusion criteria (one publication was an English-language article that included two relevant studies performed in China, and one publication provided complete information on two relevant mifepristone dosages) (Fig. 2) [8–18]. Women were generally assessed 1–2 weeks after mifepristone and those with a continuing pregnancy at that time underwent surgical abortion. Table 1 shows for each study the mifepristone regimen used, the gestational age limit, when the follow-up visit occurred, the proportion of pregnancies that had a complete abortion after mifepristone alone and the proportion of pregnancies that were continuing at the follow-up visit. The continuing pregnancy proportions ranged from 8% to 46% with the different regimens.

4. Discussion

We found only one small case series that evaluated a treatment aimed at reversing the effects of mifepristone. The proportion of pregnancies that continued after this treatment was 57–67%, but the 95% CI of this estimate was wide, ranging from 25% to 90% [7]. The study was of poor quality with few details.

Due to the limited information in the article [7], one cannot directly compare the results of this single small series to the continuing pregnancy rate after mifepristone alone, which was as high as 46% in one of the clinical trials [15]. In the report by Delgado and Davenport [7], women presented 7–48 h after mifepristone ingestion, and, except for two cases, the patient had a live embryo at the time of treatment. In order to calculate the proportion of women with a continuing pregnancy seeking this treatment, which would be comparable to the proportion of continuing pregnancies after mifepristone alone, one must know how many women requested treatment and were found to already have an embryonic demise or incomplete abortion. It is reasonable to suppose that women who have an ongoing pregnancy 1–2 days after mifepristone are more likely to have pregnancies that continue to term with no further treatment. It is also possible that some of the continuing pregnancies noted 1–2

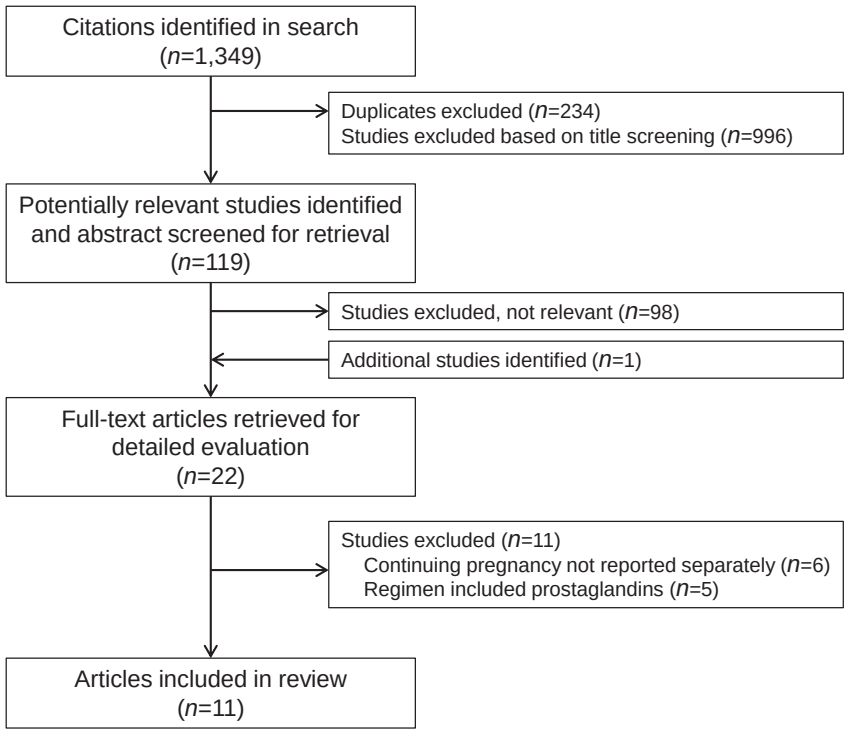

Fig. 2. Summary of study selection process for continuing pregnancy following administration of mifepristone alone for medical abortion.

weeks after treatment in the studies of mifepristone alone may have aborted if the period of follow-up were longer.

Although the dose of mifepristone was not noted in the report by Delgado and Davenport [7], women likely received 200 mg, which is the dosage recommended by ACOG and SFP and most often used by providers in the US [1,19]. Most of the studies of mifepristone alone used a higher dose, and the one study that compared 600 mg to 200 mg found a higher proportion of continuing pregnancies with 200 mg [18]. In addition, none of the studies of mifepristone alone included women pregnant beyond 56 days, while the report by Delgado and Davenport [7] included women up to 11 weeks gestation. In the first trimester, the risk of continuing pregnancy after medical abortion increases as gestational age advances [15,20].

Progesterone is used for other indications during pregnancy. Injections of 17a-hydroxyprogesterone caproate or administration of vaginal progesterone suppositories or

Table 1
Studies reporting the proportion of women with continuing pregnancies following administration of mifepristone alone for medical abortion

Study	Mifepristone oral dose	*N*	Gestational age limit	Follow-up visit (number of days after mifepristone)	Complete abortion	Continuing pregnancy at follow-up visit (%, 95% CI)
Birgerson 1988 [9]	10, 25 or 50 mg twice daily for 7 days	153	49 days	8–10 days	67%	27% (20–34%)
Cameron 1986 [8]	150 mg daily for 4 days	20	56 days	14 days	60%	25% (11–47%)
Carol 1989 [17]	600 mg (single dose)	50	39 days	NS	80%	12% (6–24%)
Grimes 1988 [10]	600 mg (single dose)	50	49 days	14 days	88%	10% (4–21%)
Kovacs 1984 [11]	25–100 mg twice daily for 4 days	36[a]	42 days	14 days	61%	8% (3–22%)
Maria 1988a [16]	600 mg (single dose)	149[a]	42 days	7 days	88%	9% (6–15%)
Maria 1988b [18]	600 mg (single dose)	174	49 days	7 days	84%	11% (8–17%)
Maria 1988b [18]	200 mg (single dose)	30	49 days	7 days	63%	23% (12–41%)
Somell 1990 [12]	600 mg (single dose)	70	42 days	7 days	80%	17% (10–28%)
Swahn 1989 [13]	25 mg twice daily for 4 days	14	49 days	14 days	57%	36% (16–61%)
Ylikorkala 1989 [14]	600 mg (single dose)	47[b]	43 days	14 days	70%	11% (5–23%)
Zheng 1989 [15]	600 mg (single dose)	204	42 days	7 days	65%	31% (25–38%)
Zheng 1989 [15]	600 mg (single dose)	95	49 days	7 days	53%	46% (37–56%)

NS, not specified.

[a] One additional participant was later found to have an ectopic and is excluded from the total here.

[b] Three additional participants had a missed abortion at time of treatment and are excluded from the total here.

gel may be used for prevention of preterm birth among women at high risk of early delivery, generally weekly from 16 weeks to 36 weeks gestation [21]. Progesterone supplementation is also used with assisted reproductive technologies that involve treatment with a gonadotropin-releasing hormone (GnRH) analog, agonist or antagonist, which may interrupt the normal functioning of the corpus luteum [22]. Progesterone in oil injections or vaginal suppositories or gel may be used for this purpose, but treatment is generally stopped after 9–12 weeks gestation, by which time the trophoblast is the primary source of progesterone. Progesterone is not associated with an increased risk of congenital anomalies, including genital abnormalities. Adverse events associated with progesterone injections include injection site swelling or irritation [23], as well as the potential of allergies to the yam, soy or peanut used in manufacturing or compounding the medication [21].

However, the evidence supporting the use of progesterone early in pregnancy after GnRH treatment or to prevent preterm birth is not directly applicable to the situation after mifepristone treatment. Mifepristone blocks the progesterone receptor with a higher affinity than progesterone itself [24]. Women treated with mifepristone for abortion have normal pregnancies with high progesterone levels, and it is not clear that adding more progesterone would counteract the effect of the receptor blockade. A recent randomized controlled trial found that insertion of an etonogestrel contraceptive implant, a very potent progestin, immediately after ingestion of mifepristone did not reduce the effectiveness of the medical abortion regimen compared to delayed insertion after abortion completion [25], confirming the findings of a previous pilot study [26]. In addition, the duration of treatment that women received in the report by Delgado and Davenport [7] was more consistent with preterm labor prevention (albeit with an unproven regimen). It also far exceeded the expected duration of action of mifepristone since the drug is undetectable in humans 10 days after ingestion of a 200-mg dose [27].

The evidence to date does not suggest an elevated risk of congenital malformations after mifepristone administration alone. A recent prospective study from France reported on 46 pregnancies exposed to mifepristone only [28]. Two major malformations occurred among 38 continuing pregnancies (5.3%), which, based on these small numbers, does not appear to be significantly elevated above the expected proportion of about 3%. While more prospective data are needed, information about the low risk of congenital malformations after mifepristone exposure should be given to women who decide to continue a pregnancy after taking the drug.

The clinical use and new state laws concerning abortion "reversal" raise serious ethical concerns. The limited data on mifepristone reversal grew out of the anecdotal experiences of physicians who performed experimental treatment on pregnant women, without usual research safeguards. Delgado and Davenport [7] do not report that their study had an ethics board or institutional review board (IRB) approval. Case reports involving retrospective analysis of three or fewer cases do not generally require IRB oversight, although institutions or journals may require IRB review to determine that the report is exempt. While Delgado and Davenport [7] published their findings as a "case report," their study is clearly "research" as defined in federal policy. Federal regulations define research as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge [29]." The report clearly extends into the realm of research, whether measured by its prospective nature, the number of patients on which it reports, its attempt to assess a specific new treatment regimen or the suggestion that the data produced be used to guide treatment of other women. In recognition of the report's limitations, Delgado and Davenport [7] themselves called for further clinical trials before routine use of their protocol. The new laws in Arizona and Arkansas have now bypassed the research process, in effect making all women who undergo this treatment subjects in an uncontrolled, unmonitored experiment.

Providing evidence-based care is part of how physicians meet their beneficence-based obligations to patients, and therefore, it is a *moral* as well as a clinical mandate to base care on accepted scientific fact. The new laws compel physicians to say things that may contradict their clinical knowledge and judgment. Some physicians will not be able to do so in good conscience; they may feel that suggesting unproven treatment or suggesting that a woman can begin an abortion with uncertainty about her decision contradicts their duty to do no harm.

Women rarely change their minds after beginning a medical abortion. According to reports that physicians are required to submit to the drug's manufacturer, between 2000 and 2012, less than 0.004% of women taking mifepristone in the US later chose to continue the pregnancy (personal communication, Danco Laboratories). In such a case, a woman should be counseled that there is a reasonable chance (10–45%) that the pregnancy will continue. We found no credible evidence that using medication after ingestion of mifepristone is better than expectant management in assuring a continuing pregnancy; suggesting otherwise is scientifically untenable. Legislative interference in the patient–physician relationship is unwarranted and dangerous [30]. In the case of recent Arizona and Arkansas laws, this interference transforms an unproven therapy into law, bases law on methodologically flawed research and in effect turns unethical experimentation on pregnant women into legislative mandate. These features of mifepristone reversal represent an affront to responsible research conduct and to the ethical practice of medicine.

Acknowledgments

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EXHIBIT G

for all disclosures closer to strict scrutiny.

The Court's approach in *NIFLA*, as the dissent noted, "could radically change prior law, perhaps placing much securities law or consumer protection law at constitutional risk." Many health laws could be similarly threatened. Already a lower court has preliminarily enjoined Food and Drug Administration warning labels for cigars on the basis of *NIFLA*.[5] Whether that injunction holds, and whether other health laws will be struck down on First Amendment grounds, remains to be seen. What is clear is that the Court has created new uncertainty, and invited new litigation, regarding numerous health laws that were once assumed to be constitutional.

An audio interview with Prof. Parmet is available at NEJM.org

Disclosure forms provided by the authors are available at NEJM.org.

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Abortion "Reversal" — Legislating without Evidence

Daniel Grossman, M.D., and Kari White, Ph.D., M.P.H.

Women up to 10 weeks pregnant who are having a medication abortion generally take one dose of mifepristone, which blocks the progesterone receptor, followed within 48 hours by a dose of misoprostol, a prostaglandin that causes cervical dilation and uterine contractions, leading to expulsion of the pregnancy tissue. Four states (Arkansas, Idaho, South Dakota, and Utah) require abortion providers to tell their patients about treatment that may reverse the effect of mifepristone if they change their mind after starting a medication abortion. So-called abortion reversal involves administering repeated doses of progesterone. Since 2017, other states have proposed similar bills and the California Board of Registered Nursing approved a course on medication-abortion reversal for continuing-education credit. This trend is troubling because of the lack of medical evidence demonstrating the safety and efficacy of the treatment; laws promoting it essentially encourage women to participate in an unmonitored research experiment.

When states began passing laws on abortion reversal, the only published report on this treatment was a case series involving seven patients. A systematic review we coauthored in 2015 found no evidence that pregnancy continuation was more likely after treatment with progesterone as compared with expectant management among women who had taken mifepristone.[1] Our review found that the proportion of continuing pregnancies after mifepristone alone varied from 8% to 46% in published studies.

Recently, Delgado et al. published a case series involving 754 patients who underwent reversal treatment in the United States and several unnamed countries.[2] After excluding 27% of patients for various reasons, they report that 47% had a live birth. The authors conclude that reversal treatment is effective, citing the higher proportion of continuing pregnancies in their study as compared with a historical control rate of 25% of women who had continuing pregnancies after taking mifepristone alone. This estimate comes from Maria et al., the only published report that examined rates of pregnancy continuation after a single 200-mg dose of mifepristone,[3] which is the dose most commonly used in current medication-abortion regimens. This study, which included 30 women who were up to 7 weeks pregnant, 25 of whom were no more than 6 weeks pregnant, found that 23% had continuing pregnancies 7 days later.

It is difficult to compare the results from Delgado et al. with data on mifepristone alone for several reasons. In the Delgado study, some providers performed ultrasonography in patients presenting for reversal and excluded those found to have embryonic death. These patients were removed from the denominator of the proportion of women with continuing pregnancies, which could have contributed to the higher success rate for reversal treatment — especially at gestational ages of more than 6 weeks, when cardiac activity is more apparent. In addition, the authors excluded patients who were lost to follow-up before 20 weeks, which probably exaggerated the treatment's reported success.

Percentage of Women with Continuing Pregnancies after Taking 200 mg Mifepristone with or without Progesterone.*				
Treatment	Total No. of Pregnancies	Continuing Pregnancies	Percentage of Continuing Pregnancies (95% CI)	P Value
Gestational age ≤6 wk				
Mifepristone followed by progesterone	189	71	38 (31–45)	0.119
Mifepristone alone	25	5	20 (9–39)	
Gestational age ≤7 wk				
Mifepristone followed by progesterone	291	121	42 (36–47)	0.076
Mifepristone alone	30	7	23 (21–41)	

* Data are from Delgado et al.[2] and Maria et al.[3] Maria et al. report a total of seven continuing pregnancies in the sample of 30 women who were 7 weeks pregnant or less. There were two abortion failures among the five women who were between 6 and 7 weeks pregnant, but whether these were continuing pregnancies is unclear. We therefore made the conservative assumption that five of the seven continuing pregnancies occurred among the 25 women who received mifepristone at 6 weeks' gestation or less and that the two failures that occurred among those who were between 6 and 7 weeks pregnant were both continuing pregnancies.

Gestational ages in Delgado et al. (up to 9 weeks) also differed from those in Maria et al. As Delgado et al. note, pregnancy continuation is more common with advanced gestation; therefore, it is important to compare groups of similar gestational age. We analyzed the effectiveness of reversal treatment by comparing rates of continuing pregnancy among women who were up to 6 or 7 weeks pregnant in the two studies.

Among women who were up to 6 weeks pregnant, 38% (95% confidence interval [CI], 31 to 45) of those who received reversal therapy had a continuing pregnancy.[2] This proportion was not significantly different from the 20% (95% CI, 9 to 39) of women who had a continuing pregnancy after taking mifepristone alone (P=0.119) (see table).[3] The rates of pregnancy continuation were also not significantly different when we included women who were up to 7 weeks pregnant, despite the fact that the reported success rate for reversal therapy was most likely an overestimate at 7 weeks because some patients were excluded from treatment after ultrasound screening for embryonic viability. Because there are no published data on rates of pregnancy continuation after a 200-mg dose of mifepristone alone at more than 7 weeks' gestation, we cannot evaluate the effectiveness of reversal treatment beyond this gestational age.

The safety data presented by Delgado et al. are minimal. No adverse events were reported among pregnant women, but it is unclear whether such data were routinely collected. The reported data on birth defects and preterm birth are generally reassuring; given the range of progesterone regimens used and the lack of reporting by regimen, however, it is difficult to draw conclusions about the treatment's safety. Data from a registry in France suggest that exposure to mifepristone alone does not increase the risk of birth defects.[4]

Equally unclear is the demand for reversal treatment. Since participants in the study by Delgado et al. were recruited from several unnamed countries over a period of 4 years, it is impossible to estimate what proportion of patients undergoing medication abortion is represented by this sample. According to data obtained from Danco Laboratories, the U.S. manufacturer of mifepristone, less than 0.004% of patients who took mifepristone between 2000 and 2012 ended up deciding to continue their pregnancies.[1] Other research indicates that decisional certainty among women having an abortion is high — and higher than it is among patients making other decisions about medical treatment.[5]

Still, efforts should be made at the time of preabortion counseling to identify women who may be conflicted and to provide additional support to help them make an informed decision. Allowing patients to take mifepristone at home, which has been permitted since the drug's label was updated in 2016, may reduce the already small number of women who change their mind by giving patients more control over where and when they take the medication. But for patients who do change their mind after taking mifepristone, what is the best course of action? If a woman changes her mind within an hour after taking the drug, vomiting should be induced. Beyond that time frame, we believe the pregnancy should be carefully followed.

One could argue that the demand for abortion reversal treatment is so low that additional research is not justified. But if

researchers do perform additional studies, it is critical that such studies be rigorously designed and conducted in an ethical manner. Clinical equipoise exists for this question, since there is no evidence that treatment is superior to doing nothing. In such cases, a randomized, placebo-controlled trial is the most appropriate study design. For now, any use of reversal treatment should be considered experimental and offered only in the context of clinical research supervised by an institutional review board (IRB). Delgado et al. obtained IRB approval for their retrospective data analysis, but it is not clear that approval was obtained in advance for their experimental treatment protocol. In fact, the study was retracted temporarily because of concerns raised about what the authors initially described as an IRB "waiver."

We believe that states' mandating that health care providers give patients information about an unproven and experimental therapy is a disturbing intrusion into the relationship between physicians and their patients. Additional states will undoubtedly consider such legislation, despite the lack of evidence for abortion reversal treatment. We should all be concerned when politicians recommend treatment options over the advice of medical professionals.

Disclosure forms provided by the authors are available at NEJM.org.

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Extensively Drug-Resistant Typhoid — Are Conjugate Vaccines Arriving Just in Time?

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In Hyderabad, Pakistan, an outbreak of extensively drug-resistant (XDR) *Salmonella enterica ssp. enterica* serovar Typhi, resistant to chloramphenicol, ampicillin, trimethoprim–sulfamethoxazole, fluoroquinolones, and third-generation cephalosporins, was recognized in November 2016 and has now spread to Karachi, home to more than 14 million people. More than 1000 cases have been confirmed by blood culture; since most typhoid cases are treated empirically, however, the true number of cases is probably many times greater. The outbreak is being caused by the H58 clade, a multidrug-resistant haplotype of *S.* Typhi that is common in Asia and areas of Africa. The H58 *S.* Typhi involved in the outbreak contains a chromosomally integrated antimicrobial-resistance cassette imparting resistance to chloramphenicol, ampicillin, and trimethoprim–sulfamethoxazole, and the XDR variant also contains an IncY plasmid that carries not only the fluoroquinolone-resistance gene *qnrS* but also the CTX-M-15 gene *bla* that mediates resistance to ceftriaxone.[1] *S.* Typhi already causes invasive disease in 12 million to 22 million people each year, many of whom live in South and Southeast Asia, and the emergence of an XDR variant in this densely populated area is extremely worrisome.[2]

Prior to the advent of antimicrobial therapy, case fatality rates for typhoid fever exceeded 20% in many areas, since untreated disease led to complications such as intestinal perforation. In 1948, the first effective antimicrobial therapy for typhoidal salmonella, chloramphenicol, ushered in a new era in the management of enteric fever (see timeline). Within 2 years, however, the first clinical isolate resistant to chloramphenicol was reported. But resistance was relatively uncommon, and chloramphenicol remained the mainstay of therapy for the next two decades. In the early 1970s, outbreaks of chloramphenicol-resistant typhoid with evidence of horizontal transfer of resistance genes were reported around the world. Ampicillin and trimethoprim–sulfamethoxazole emerged as alternative, albeit possibly inferior, therapies for chloramphenicol-resistant enteric fever. By the late 1980s, resistance to all three antibiotics (multidrug-resistant typhoid) was increasingly